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(71) Applicant: **SUMITOMO CHEMICAL COMPANY, LIMITED**
Kitahama 4-chome 5-33
Chuo-ku
Osaka 541 (JP)

(72) Inventor: **Hayashi, Koji**
14-7, Mefu 2-chome
Takarazuka-shi,
Hyogo-ken (JP)
Inventor: **Sakaki, Toshiyuki**
1-30-68, Higashitoyonaka-cho
Toyonaka-shi,
Osaka-fu (JP)
Inventor: **Yabusaki, Yoshiyasu**
6-2-1, Minatojimanakamachi,
Chuo-ku
Kobe-shi,
Hyogo-ken (JP)
Inventor: **Komai, Koichiro**
4-9-17, Sakuragaoka
Minoo-shi,
Osaka-fu (JP)
Inventor: **Kaneko, Hideo**
63, Koyamaitakura-cho,
Kita-ku
Kyoto-shi,
Kyoto-fu (JP)
Inventor: **Nakatsuka, Iwao**
3-8-14, Hinomine,
Kita-ku
Kobe-shi,
Hyogo-ken (JP)

(74) Representative: **VOSSIUS & PARTNER**
Postfach 86 07 67
D-81634 München (DE)

(54) Method for safety evaluation of chemical compound using recombinant yeast expressing human cytochrome P450.

(57) There is disclosed a method for evaluation of the safety of a chemical compound, which includes the steps of: (a) reacting a chemical compound with recombinant yeast cells expressing, or in other words producing, human cytochrome P450 molecular species P450 1A2, P450 2C9, P450 2E1 and P450 3A4 together with a yeast NADPH-P450 reductase, which may be in the form of a fused enzyme with each of said human cytochrome P450 molecular species, or with the cell free extracts of the yeast cells; and (b) analyzing the resulting metabolite to determine the safety of the compound. According to this method, it can be determined whether a test compound will be converted into a carcinogenic or mutagenic form through the metabolism in the human liver, and whether the test compound or its metabolite has mutagenicity.

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The present invention relates to a method for evaluation of the safety of a chemical compound using recombinant yeasts expressing human cytochrome P450.

The cytochrome P450 is an enzyme catalyzing the mono-oxygenation of a substance in the human liver.

It is known that recombinant human cells expressing heterogeneous human cytochrome P450 species have been used for determination of metabolisms and toxicities of chemical substances. However, this method is unsatisfactory as a method of evaluation of the safety of chemical compounds partly because the kinds of the human cytochrome P450 species expressed by the cells and the levels of the expression are so limited that the amount of metabolite obtained is not enough for determination of the metabolism and toxicity, and partly because it requires not only a high density culture technique but a high cultivation cost. Accordingly, there has been a great demand for developing an advantageous method.

As a result of the extensive study, the present inventors have found that yeasts are particularly suitable as hosts for production of human cytochrome P450 and yeast NADPH-P450 reductase to be used in in vitro determination of metabolisms and toxicities of chemical substances because yeasts grow so rapidly and can stably express both the human cytochrome P450 and yeast NADPH-P450 reductase at high expression levels to provide sufficient amounts of the metabolites in a short period of time, thereby enabling a precise and quick analysis of the metabolites.

Moreover, they have also found that, despite that there are a considerable number of human cytochrome P450 molecular species, the human metabolic system for chemical compounds can be reproduced in vitro when at least four human cytochrome P450 molecular species, i.e., human cytochrome P450 1A2, P450 2C9, P450 2E1 and P450 3A4, are combined.

Thus, the present invention provides a method for evaluation of the safety of a chemical compound, which comprises the steps of:

(a) reacting a chemical compound with recombinant yeast cells expressing, or in other words producing, human cytochrome P450 molecular species P450 1A2, P450 2C9, P450 2E1 and P450 3A4 together with a yeast NADPH-P450 reductase, which may be in the form of a fused enzyme with each of said human cytochrome P450 molecular species, or with the cell free extracts of the yeast cells; and

(b) analyzing the resulting metabolite to determine the safety of the compound.

The present invention further provides a method for determination of the human metabolite of a chemical compound, which comprises the steps of:

(a) reacting a chemical compound with recombinant yeast cells producing human cytochrome P450 molecular species P450 1A2, P450 2C9, P450 2E1 and P450 3A4 together with a yeast NADPH-P450 reductase, which may be in the form of a fused enzyme with each of said human cytochrome P450 molecular species, or with cell free extracts of the yeast cells; and

(b) identifying the resulting metabolite.

Figs. 1 to 4 show various primers for cloning human P450 genes.

Fig. 5 shows a synthetic linker for human P450 gene cloning.

Fig. 6 shows a method of constructing yeast expression plasmids for human P450 1A2.

Fig. 7 shows a method of constructing yeast expression plasmids for human P450 2C9.

Fig. 8 shows a method of constructing yeast expression plasmids for human P450 2E1.

Fig. 9 shows a method of constructing yeast expression plasmids for human P450 3A4.

Fig. 10 shows a method of constructing yeast expression plasmids for human P450 1A1.

Fig. 11 shows a method of constructing yeast expression plasmids for human P450 2A6.

Fig. 12 shows a method of constructing yeast expression plasmids for human P450 2B6.

Fig. 13 shows a method of constructing yeast expression plasmids for human P450 2C8.

Fig. 14 shows a method of constructing yeast expression plasmids for human P450 2C18.

Fig. 15 shows a method of constructing yeast expression plasmids for human P450 2C19.

Fig. 16 shows a method of constructing yeast expression plasmids for human P450 2D6.

Fig. 17 shows a method of constructing a yeast expression plasmid containing an artificial fused enzyme gene.

Fig. 18 shows a method of constructing a yeast expression plasmid using a GAPDH promoter.

According to the present invention, it can be determined whether a test compound will be converted into a carcinogenic or mutagenic form through the metabolism in the human liver, and whether the test compound or its metabolite has mutagenicity.

Thus, the present invention provides a method for evaluation of safety of a chemical compound, and a method for determination of the human metabolite of a chemical compound.

Human Cytochrome P450 and Their Genes

The yeasts capable of expressing, or producing, said enzymes can be obtained by transforming them with expression plasmids containing genes encoding said enzymes with a conventional recombinant DNA method.

The human P450 molecular species to be used in the present invention include at least four human cytochrome P450 molecular species, i.e., human cytochrome P450 1A2, P450 2C9, P450 2E1 and P450 3A4. The genes encoding these essential human cytochrome P450 molecular species and yeast NADPH-P450 reductase are reported in Nucleic Acids Res., 14, 6773-6774, 1986; J. Biochem., 102, 1075-1082, 1987; J. Biol. Chem., 261, 16689-16697, 1986; DNA, 7, 79-86, 1988; and J. Biochem., 103, 1004-1010, 1988.

Although the kinds of P450 molecular species present in human liver vary among the race and individuals, the combination of said human P450 molecular species includes at least about 85% (molar ratio) of the total amount of the human P450 molecular species present in the human liver. Hence, the present method using the said combination of human P450 molecular species can accurately reproduce the human liver metabolism in vitro.

The combination of these P450 molecular species may optionally be varied, taking into account of the amounts of these P450 molecular species in the liver: the amount of P450 3A4 present in the human liver is about 35±10% of the total amount of the human P450 molecular species; P450 2C9 about 25±10%; P450 1A2 about 23±10%; and P450 2E1 about 17±10%.

In addition to the above-mentioned combination, human P450 molecular species P450 2A6, P450 2C19 and/or P450 2D6 (Biochemistry, 29, 1322-1329, 1990; Biochemistry, 30, 3247-3255, 1991; Am. J. Hum. Genet., 45, 889-904, 1989) may also be added. In this case, the combined human P450 molecular species covers at least 90% of the total amount of the human P450 molecular species present in the human liver.

The in vitro human metabolic system that reproduces accurately the human metabolism of a chemical compound, and can represent the differences among races and individuals can be obtained when these human P450 molecular species are properly combined, taking into account of the amounts of these species in the liver.

Furthermore, at least one human cytochrome P450 molecular species selected from the group of P450 1A1, P450 2B6, P450 2C8 and P450 2C18 (Science, 228, 80-83, 1985; Biochemistry, 28, 7340-7348, 1989; Nucleic Acids Res., 15, 10053-10054, 1987; Biochemistry, 30, 3247-3255, 1991) may be added to said human cytochrome P450 molecular species to reproduce in vitro the metabolism of the human liver more accurately.

The nucleotide sequences coding for the human P450 molecular species are disclosed in SEQ ID NOs: 1 to 38.

Cloning of Genes

The genes coding for the human cytochrome P450 molecular species are known and can be obtained by the conventional cloning methods.

For example, they may be obtained by:

(i) preparing a mRNA fraction containing the mRNA of the gene coding for human cytochrome P450 molecular species;

(ii) preparing a cDNA from the mRNA fraction using reverse transcriptase;

(iii) preparing a cDNA library by inserting said cDNA into a pharge vector or a plasmid vector; and

(iv) cloning the gene coding for the human cytochrome P450 molecular species from the cDNA library obtained above or from a commercially available human liver-derived cDNA library using a DNA fragment having an identical sequence to some part of the desired gene or an antibody reactive to the protein produced by the gene.

The gene may also be obtained from the above-described cDNA library by the PCR method.

The gene coding for yeast NADPH-P450 reductase may be obtained by the same method as used for cloning of the genes coding for human P450 molecular species. More specifically, the gene may be obtained by such a known method as described in the Japanese Patent Laid-open Publication No. 62-19085.

Construction of Yeast Expression Plasmids

The yeasts capable of expressing said enzymes can be obtained by transforming them with expression plasmids containing genes encoding said enzymes with a conventional recombinant DNA method.

The yeast expression plasmid having a gene coding for human P450 molecular species and a gene coding for the yeast NADPH-P450 reductase can be constructed by using a conventional recombinant DNA method.

As to the promoter to be used for construction of the expression plasmids for the yeast of the present invention, there is no particular restriction so long as the promoter can be used in usual expression systems for yeasts, and a promoter of a yeast alcohol dehydrogenase gene (hereinafter referred to as ADH promoter), glyceraldehyde-3-phosphate dehydrogenase promoter (hereinafter referred to as GAPDH promoter), and phosphoglycerate kinase (hereinafter referred to as PGK promoter) are preferably used in the present invention.

The ADH promoter can be prepared by a usual genetic engineering method, for example, from a yeast expression vector pAAH5 possessing a yeast ADH1 promoter and terminator ("Methods in Enzymology" by Ammerer et al., vol.101, pp.192-201). The yeast ADH1 promoter is described in the U.S. Patent No. 299,733 to Washington Research Foundation and it requires patent license from the patentee in a case of using the same for an industrial or commercial purpose.

The yeast expression plasmid having both a gene coding for human P450 molecular species and a gene coding for the yeast NADPH-P450 reductase can be constructed by, for example, inserting an NotI fragment prepared from yeast expression vector pAAH5N possessing the ADH promoter and terminator (Japanese Patent Laid-open Publication No. 2-211880) to an NotI site of plasmid pARRN possessing a gene coding for yeast NADPH-P450 reductase (Japanese Patent Laid-open Publication No. 2-211880) and then inserting cDNA coding for the human P450 molecular species to the HindIII site of the thus obtained plasmid pAHRR. Moreover, a vector obtained by exchanging a Hind III site of pAAH5N with other restriction enzyme site may be used for the same purpose.

In the present invention a gene coding for an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase can also be used. The artificial fused enzyme can catalyze mono-oxygenation reaction and the efficiency of the electron transfer from NADPH is so improved that the activity of the mono-oxygenation reaction is much enhanced. Accordingly, a great amount of metabolic products can be obtained in a shorter period of time, enabling accurate analysis.

The fused gene comprises a gene coding for the human cytochrome P450 molecule on the 5'-terminal and a gene coding for the yeast NADPH-P450 reductase on 3'-terminal.

The gene coding for such an artificial fused enzyme can be constructed by ligating a gene coding for a human cytochrome P450 species and a gene coding for yeast NADPH-P450 reductase by a conventional recombinant DNA method, and the constructed gene is usually inserted to the Hind III site of the yeast expression vector pAAH5N having ADH promoter and ADH terminator described in the Japanese Patent Laid-open Publication No. 2-211880.

Transformation of Yeast

The yeast cells expressing the human P450 molecular species and yeast NADPH-P450 reductase or yeast cells expressing an artificial fused enzyme comprising human P450 molecular species and NADPH-P450 reductase can be obtained by introducing the thus constructed yeast expression plasmid into a yeast by a known method such as a protoplast method or a method using alkaline metal salt (LiCl).

In the present invention, two or more expression plasmids may optionally be introduced into a single strain of yeast so that the yeast can express two or more molecular species simultaneously.

As the hosts, Saccharomyces cerevisiae is used in the method of the present invention, in particular, Saccharomyces cerevisiae AH22 (ATCC 38626) is preferably used.

Reaction of Test Compound

In the method of the present invention, a test compound is reacted with a mixture of at least said four human P450 molecular species, or separately with each of the said four human P450 molecular species in the presence of the yeast NADPH-P450 reductase.

Alternatively, it may be first reacted with one or more of the essential human P450 molecular species, and then with a mixture of, or separately with the rest of them; each of the reactions is carried out in the presence of the yeast NADPH-P450 reductase.

The reaction is carried out by reacting a test compound with the yeast obtained by the transformation with an expression plasmid containing a gene encoding a human P450 molecular species and a gene encoding yeast NADPH-P450 reductase, or a fused gene encoding a fused enzyme of a human P450 molecular species and a yeast NADPH-P450 reductase, or with the cell free extracts of the yeast cells.

In the reaction of a test compound with the enzymes of the present invention, living yeast cells and their cell free extracts are usually used.

As the cell free extracts, subcellular fraction of cells containing microsomal fractions, or fractions containing both microsome and cytoplasm is used. The cell free extracts or fractions can be prepared, for example, by a known method (DNA, Vol.4, No. 3, pp.203-210 (1985)).

However, the present invention can be preferably carried out with the cell free extracts, especially with microsomal fractions of the cells. But, when biological analytic method is used to determination of the mutagenicity or carcinogenicity, fractions containing microsome and cytoplasm are preferably used.

The reaction can be conducted by adding a test compound to a culture solution or a buffer solution of yeast cells or cell free extracts, and the resultant solution is usually incubated at a temperature, for example, at about 10 • C to 40 • C, for about 0.1 to 48 hours.

The amounts of the yeast cells or cell free extracts and the compound vary depending on the conditions such as reaction temperature, reaction time and the kind of the test compound to be used.

For instance, the amount of the yeast cells to be used in the solution is preferably from about 10^5 to about 10^{10} per 1 ml of the solution , preferably, from about 10^7 to about 10^8 per 1 ml of the solution. When cell free extracts are used, from about 10^{10} to about 10^{15} of P450 molecules per 1 ml of the solution, preferably from about 10^{12} to about 10^{13} of P450 molecules per 1 ml of the solution is usually used.

The amount of the compound to be added is preferably within a range of from about 0.01 μmol to about 1μmol per 1 ml of the solution.

The above ranges may be optionally varied, if necessary.

Determination of Metabolites

The metabolites present in the reaction solution can then be subjected to elucidation of the chemical structures and the measurement of their amounts. The analysis of the chemical structure can be conducted by known methods ("Guide to Apparatus Analysis (2)", edited by Jiro Shiokawa et al., (revised edition) first print, issued from Kagaku Dojin (1985); "Spectral Identification for Organic Compound" by R.M. Silverstein, fourth edition, third print, issued from Tokyo Kagaku Dojin (1984)).

From the results of the analysis of the metabolites, it can be determined whether the tested compound will be detoxicated or metabolized into a carcinogen in the human liver when administered.

Determination of Toxic Effects of Metabolites

The toxic effects, in particular mutagenicity, of the resulting metabolites can be determined by a conventional biological analytic method such as the Ames Test. For example, the metabolites present in the reaction solution are allowed to react with mutant bacteria such as histidine requiring Salmonella strain (Salmonella typhimurium (his-)), or tryptophan requiring Escherichia coil (Escherichia coil (trp-)), and then determine whether the metabolites cause the back mutation of the bacteria whether the colonies of revertant which is not requiring the amino acid (His + or Trp +) are formed, and, if formed, how many colonies. In place of the bacteria, mammalian cells such as MCL-5 cells, which are sensitive to cell toxicity of a chemical compound (U.S. Patent No. 4,532,204), can be used.

In this method, the compounds that cause the back mutation will be judged to be mutagenicity test-positive.

It is also possible to simultaneously proceed the step (a) of reacting the test compound with the yeast cells or the cell free extracts, and the step (b) of analyzing the metabolites present in the reaction solution.

The mutagenicity of arylamine derivatives, which are known to be metabolized by the liver into a mutagens, can be examined by the biological analytic method. For example, the mutagenicity of 2-aminoanthrathene can be detected at the concentration of about 0.1 μg of 2-aminoanthrathene when 20 pmol of P450 1A2, which is active specifically to 2-aminoanthrathene, is used (Table 1).

In the present invention, a metabolic probe for a human P450 molecular species can be obtained.

If a certain chemical compound is converted by a particular human P450 molecular species into a specific metabolite, the amount of such a human P450 molecular species can be determined by detecting such a metabolite in excretions such as blood or urine of a living body who has been administered the compound, and such a compound is called a metabolic probe.

In the present invention, such a metabolic probe can be obtained by screening the metabolites obtained by reacting chemical compounds with the yeasts of the present invention.

Examples

The present invention will be further illustrated by the following examples, which are not to be construed to limit the scope thereof.

Preparation of cDNA coding for human P450 molecular species

cDNA coding for human P450 molecular species were obtained from commercially available human liver cDNA library (Clontech Co.) by the PCR method using primers for cloning human P450 genes as shown in Figs. 1 to 4, and a method using a synthetic linker for human P450 gene cloning as shown in Fig. 5. Thus obtained nucleotide sequences for the cDNA and the deduced amino acid sequences are shown in the sequence listing.

Relationship between SEQ ID NOs and human P450 molecular species are as follows:

1. The essential human cytochrome P450 molecular species for the present invention.

(1) SEQ ID NO: 1	1A2
(2) SEQ ID NO: 3	2C9
(3) SEQ ID NO: 5	2E1
(4) SEQ ID NO: 7	3A4

2. Auxiliary Human cytochrome P450 molecular species

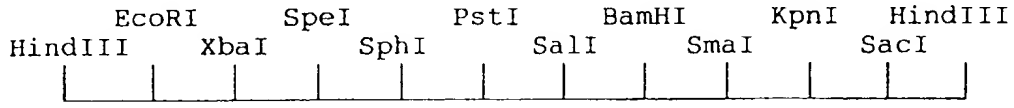
(1) SEQ ID NOs: 9, 11 and 13	1A1
(2) SEQ ID NOs: 15 and 17	2A6
(3) SEQ ID NO: 19	2B6
(4) SEQ ID NOs: 21, 23 and 25	2C8
(5) SEQ ID NO: 27	2C18
(6) SEQ ID NO: 29	2C19
(7) SEQ ID NOs: 31, 33, 35 and 37	2D6

Construction of yeast expression plasmids: p1A2 and p1A2R

Fig. 6 shows a method of constructing yeast expression plasmids for human P450 1A2. The protein coding region of P450 1A2 gene of about 1.5 kb excluding about 40 bp at the 5'-terminal was amplified by the PCR method using the primers shown in Fig. 1. The resultant fragment of about 1.5 kb was cleaved with SacI and sub-cloned to a pUC118 vector. About 40 bp at the 5'-terminal was chemically synthesized as the linkers shown in Fig. 5 and sub-cloned between the HindIII and SacI sites of the pUC118 vector. The plasmid having the 1.5 kb fragment was digested by HindIII, blunted, and then ligated with an EcoRI linker. The EcoRI-SacI fragment was prepared from the resulting plasmid and ligated into the plasmid containing the 5'-terminal 40 bp. Then, it was treated with EcoRI and blunted. A HindIII linker was inserted into the blunted fragment. The obtained fragment then cleaved with HindIII was inserted into pAAH5N and pAHRR to construct a yeast expression plasmid p1A2 for human P450 1A2, and a yeast expression plasmid p1A2R for simultaneous expression of human P450 1A2 and yeast NADPH-P450 reductase.

Construction of yeast expression plasmids: p2C9 and p2C9R

Fig. 7 shows a method of constructing yeast expression plasmids for human P450 2C9. The protein coding region of 450 2C9 gene was divided into two fragments of about 0.9 kb and about 0.6 kb, and the fragments were amplified by the PCR method using the primers shown in Fig. 1. The resultant fragment of about 0.9 kb was cleaved with PstI and sub-cloned to a pUC B vector, which was prepared by exchanging the cloning site located between the two Hind III sites, one of which was obtained by converting the EcoRI site of pUC19, with the following cloning sites:



The fragment of about 0.6 kb was incorporated between the Xbal and PstI sites of the plasmid having the 0.9 kb fragment to ligate the two segments. The KpnI site of the plasmid was blunted. An Xbal linker was inserted to the blunted plasmid. The Xbal fragment containing the coding region was cut out from the resultant fragment. A modified pUC vector, pUCAN, was constructed by replacing the EcoRI and HindIII sites with NotI sites, followed by insertion of the NotI fragment prepared from pAAH5N between the two NotI sites. The HindIII site of pUCAN vector having the ADH promoter and terminator regions in the pUC vector was blunted and inserted into pUCANX introduced with the Xbal linker. The obtained plasmid was cleaved with NotI and inserted into pAAH5N and pAHRR treated in a similar manner with NotI to construct a yeast expression plasmid p2C9 for human P450 2C9, and a yeast expression plasmid p2C9R for simultaneous expression of human P450 2C9 and yeast NADPH-P450 reductase.

Construction of yeast expression plasmids: p2E1 and p2E1R

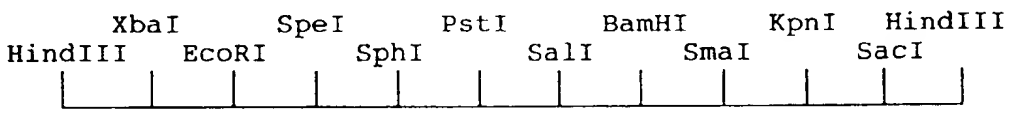
Fig. 8 shows a method of constructing yeast expression plasmids for human P450 2E1. The protein coding region of P450 2E1 gene was divided into two fragments of about 0.5 kb and about 1.0 kb, both of which were amplified by the PCR method using the primers shown in Fig. 1. The resultant fragment of about 0.5 kb was cleaved with EcoRI and BamHI and sub-cloned to a pUC118 vector. Then the fragment of about 1.0 kb was incorporated between the BamHI and SphI sites to ligate the two fragments. This was cleaved with EcoRI, and SphI, and inserted into pUC B first and then cut out with HindIII. The resultant fragment was inserted into pAAH5N and pAHRR vectors to construct a yeast expression plasmid p2E1 for human P450 2E1, and a yeast expression plasmid p2E1R for simultaneous expression of human P450 2E1 and yeast NADPH-P450 reductase.

Construction of yeast expression plasmids: p3A4 and p3A4R

Fig. 9 shows a method of constructing yeast expression plasmids for human P450 3A4. The protein coding region of P450 3A4 gene was divided into two fragments of about 0.6 kb and about 0.9 kb, both of which were amplified by the PCR method using the primers shown in Fig. 2. The resultant fragment of about 0.6 kb was cleaved with SacI and sub-cloned to a puC118 vector. Subsequently, it was cleaved with EcoRI and blunted. An Xbal linker was ligated to the blunted fragment. The fragment of 0.9 kb was cleaved with Xbal and SacI, and incorporated to the resultant fragment above, thus the two fragments were ligated. After cleaving the plasmid with SphI, it was blunted. An Xbal linker was ligated to the blunted fragment, from which the Xbal segment was cut out and inserted to an Xbal site of pUCANX. This was cut out with NotI and inserted into pAAH5N and pAHRR treated in a similar manner with NotI. Thus a yeast expression plasmid p3A4 for human P450 3A4, and a yeast expression plasmid p3A4R for simultaneous expression of human P450 3A4 and yeast NADPH-P450 reductase were constructed.

Construction of yeast expression plasmids: p1A1 and p1A1R

Fig. 10 shows a method of constructing yeast expression plasmids for human P450 1A1. The coding region for P450 1A1 protein was divided into two fragments of about 1.0 kb and about 0.5 kb and the resultant fragments were amplified by the PCR method using the primers shown in Fig. 2. Thus obtained fragment of about 1.0 kb was cleaved with Xbal and SacI and sub-cloned to a PUCA vector, which was prepared by exchanging the cloning site located between the two HindIII sites, one of which was obtained by converting the EcoRI site of pUC19, with the following cloning sites:



The amplified fragment of about 0.5 kb was sub-cloned into the HincII site of a pUC 19 vector and the resultant plasmid was then cleaved with SacI. The cleaved fragment was ligated with the plasmid having the 1.0 kb fragment. After cutting out the coding region from the thus obtained 1A1 gene with HindIII, the fragment was inserted to the HindIII site of the yeast expression vector pAAH5N having ADH promoter and terminator regions, and to the same site of vector pAHRR for simultaneous expression of P450 and yeast NADPH-P450 reductase of which gene is located upstream of the P450 gene. Thus yeast expression plasmid p1A1 for human P450 1A1 and yeast expression plasmid p1A1R for simultaneous expression of human P450 1A1 and yeast NADPH-P450 reductase were constructed.

In addition two kinds of human P450 1A1 gene fragments which were different only in a small portion of the nucleotide sequence were obtained in a similar manner and used to construct two kinds of yeast expression plasmid for human P450 1A1, p1A1 Variant 1 and p1A1 Variant 2, and two kinds of plasmids for simultaneous expression of human P450 1A1 and yeast NADPH-P450 reductase, p1A1R Variant 1 and p1A1R Variant 2.

Construction of yeast expression plasmids: p2A6 and p2A6R

Fig. 11 shows a method of constructing yeast expression plasmids for human P450 2A6. A protein coding region of P450 2A6 gene was divided into two fragments of about 0.6 kb and about 0.9 kb, both of which were amplified by the PCR method using the primers shown in Fig. 2 to yield two kinds of human P450 2A6 gene fragments which were different only in a small portion of the nucleotide sequence. The resultant fragment of about 0.6 kb was cleaved with XbaI and HincII, and sub-cloned to a pUC A vector. Then the fragment of 0.9 kb was incorporated between the HincII and KpnI sites to ligate the two fragments. The obtained fragment was cleaved with HindIII and inserted into pAAH5N and pAHRR to construct two kinds of yeast expression plasmid for human P450 2A6, p2A6 and p2A6 Variant 1, and two kinds of yeast expression plasmid for simultaneous expression of human P450 2A6 and yeast NADPH-P450 reductase, p2A6R and p2A6R Variant 1.

Construction of yeast expression plasmids: p2B6 and p2B6R

Fig. 12 shows a method of constructing yeast expression plasmids for human P450 2B6. The entire protein coding region of P450 2B6 gene was amplified by the PCR method using the primers shown in Fig. 3. The resultant fragment was cleaved with XbaI and BamHI and sub-cloned to pUC A. The resulting plasmid was partially digested with HindIII, and inserted into pAAH5N and pAHRR vectors to construct a yeast expression plasmid p2B6 for human P450 2B6, and a yeast expression plasmid p2B6R for simultaneous expression of human P450 2B6 and yeast NADPH-P450 reductase.

Construction of yeast expression plasmids: p2C8 and p2C8R

Fig. 13 shows a method of constructing yeast expressed plasmids for human P450 2C8. The entire protein coding region of the P450 2C8 gene was amplified by the PCR method using the primers shown in Fig. 3 to yield three kinds of P450 2C8 genes which were different only in a small portion of the nucleotide sequence. The resultant fragments were partially digested with XbaI, and sub-cloned to pUC A. The fragment was cleaved with HindIII and inserted into pAAH5N and pAHRR vectors to construct three kinds of yeast expression plasmids p2C8, p2C8 Variant 1 and p2C8 Variant 2 for human P450 2C8, and three kinds of yeast expression plasmids, p2C8R, p2C8R Variant 1 and p2C8R Variant 2 for simultaneous expression of human P450 2C8 and yeast NADPH-P450 reductase.

Construction of yeast expression plasmids: p2C18 and p2C18R

Fig. 14 shows a method of constructing yeast expression plasmids for human P450 2C18. The protein coding region of P450 2C18 gene was divided into two segment of about 1.4 kb and about 0.9 kb, then the both fragments were amplified by the PCR method using the primers shown in Fig. 3. The amplified fragment of about 1.4 kb was cleaved with PstI and sub-cloned to a pUC A vector. The fragment of about 0.9 kb was incorporated between the XbaI and PstI sites to ligate the two fragments. After cleaving the plasmid with SmaI, an XbaI linker was introduced. Then an XbaI fragment was prepared and inserted into the XbaI site of pUCANX. It was cleaved with NotI and inserted into pAAH5N and pAHRR treated in a similar manner with NotI to construct a yeast expression plasmid p2C18 for human P450 2C18, and a yeast expression plasmid p2C18R for simultaneous expression of human P450 2C18 yeast and NADPH-P450

reductase.

Construction of yeast expression plasmids: p2C19 and p2C19R

Fig. 15 shows a method of constructing yeast expression plasmids for human P450 2C19. Fragments a, b and c for the protein coding region of P450 2C19 gene were amplified by the PCR method using the primers No. 1, No. 2, No. 3 and No. 4, No.5 and No. 6, and No.5 and No.7 defined by SEQ ID NOs: 39-45, respectively.

Fragments e and f for the protein coding region of human cytochrome P450 2C19 were also amplified against human cytochrome P450 2C9 gene by the PCR method using the primers No. 8 to 21 having nucleotide sequences with some mutations shown by SEQ ID NOs: 46 to 59. A fragment d for the linker Nos. 1 and 2 having nucleotide sequences shown by SEQ ID NOs: 60 and 61 was obtained by directly synthesizing the DNA to cover the rest of the protein coding region of the human P450 2C19 gene. Thus the fragments covering the whole protein coding region of the human cytochrome P450 2C19 were obtained.

After the fragments a and b were treated with XhoI and BamHI, and with BamHI and PstI, both fragments were simultaneously inserted between the XhoI and PstI sites of the Blue Script(+). The fragment e was treated with XbaI and XhoI and inserted to the XbaI and XhoI sites of the plasmid having the fragments a and b to give a plasmid having the fragments a, b and e.

After the fragment c was treated with PstI and KpnI, the resulting fragment was simultaneously inserted with the linker fragment d between the PstI and EcoRI sites of the Blue Script(+). The resultant plasmid was cut with PstI and EcoRI to give a fragment containing the fragments c and d. Then this fragment was simultaneously inserted between the fragment f treated with EcoRI to the PstI and HincII sites of the aforementioned plasmid containing the fragment a, b and e. Thus a plasmid having the whole coding region of the human cytochrome P450 2C19 gene was constructed. The constructed plasmid was cut with HindIII and the resultant fragment was inserted to pAAH5N and pAHRR both of which were treated with HindIII to give a yeast expression plasmid p2C19 for expressing the human P450 2C19 and a yeast expression plasmid p2C19R for simultaneous expression of the human P450 2C19 and yeast NADPH-P450 reductase.

SEQ ID NOs and primer Nos. are as follows:

SEQ ID No: 39	Primer No. 1
SEQ ID NO: 40	Primer No. 2
SEQ ID NO: 41	Primer No. 5
SEQ ID NO: 42	Primer No. 4
SEQ ID NO: 43	Primer No. 5
SEQ ID NO: 44	Primer No. 6
SEQ ID NO: 45	Primer No. 7
SEQ ID NO: 46	Primer No. 8
SEQ ID NO: 47	Primer No. 9
SEQ ID NO: 48	Primer No. 10
SEQ ID NO: 49	Primer No. 11
SEQ ID NO: 50	Primer No. 12
SEQ ID NO: 51	Primer No. 13
SEQ ID NO: 52	Primer No. 14
SEQ ID NO: 53	Primer No. 15
SEQ ID NO: 54	Primer No. 16
SEQ ID NO: 55	Primer No. 17
SEQ ID NO: 56	Primer No. 18
SEQ ID NO: 57	Primer No. 19
SEQ ID NO: 58	Primer No. 20
SEQ ID NO: 59	Primer No. 21
SEQ ID NO: 60	Linker No. 1
SEQ ID NO: 61	Linker No. 2

Construction of yeast expression plasmids: p2D6 and p2D6R

Fig. 16 shows a method of constructing yeast expression plasmids for human P450 2D6. The protein coding region of 1.3 kb excluding about 200 bp at the 5'-terminal of P450 2D6 gene was divided into two fragments of about 0.4 kb and about 0.9 kb, and the both fragments were amplified by the PCR method. The resultant fragment of about 0.9 kb was cleaved with KpnI and sub-cloned to pUC A. For the 200 bp on the 5'-terminal, three synthetic linkers shown in Fig. 5 were used and two linkers on the 5'-terminal were incorporated into XbaI and PstI sites of a Blue Script(+) vector and then other linkers were incorporated into SmaI and PstI sites. Then fragment of about 0.4 kb obtained by the PCR method was incorporated into the PstI and HincII sites of the plasmid and then cleaved with NspV and XbaI. The resultant fragment was inserted into the plasmid containing the 0.9 kb fragment to ligate the coding region. This was cleaved with HindIII and inserted into pAAH5N and pAHRR vectors to construct a yeast expression plasmid p2D6 for human P450 2D6, and a yeast expression plasmid p2D6R for simultaneous expression of human P450 2D6 and yeast NADPH-P450 reductase.

Then three kinds of human P450 2D6 gene fragments which were different only in a small portion of the nucleotide sequence were obtained in a similar manner as described above and used to construct two kinds of yeast expression plasmids for human P450 2D6, p2D6 Variant 1, p2D6 Variant 2 and p2D6 Variant 3, and three kinds of yeast expression plasmid 2D6R for simultaneous expression of human P450 2D6 yeast and NADPH-P450 reductase, p2D6R Variant 1, p2D6R Variant 2 and p2D6R Variant 3.

Construction of yeast expression plasmid containing artificial fused enzyme gene

An expression plasmid was constructed in accordance with Fig. 17. The XbaI-XhoI fragment was amplified with plasmid p3A4 by using the primers shown in Fig. 4. On the other hand, the XhoI-HindIII fragment of about 2.1 kb was obtained from the plasmid pBFCRI (Japanese Patent Application No. 4-209226) and inserted between the XhoI and HindIII sites of a commercial vector Blue Script(+), followed by digestion with restriction enzymes XhoI and XbaI. These two fragments were simultaneously inserted to the XbaI site of the vector pUCAN, which was then digested with NotI to give a fragment of about 5.6 kb. The desired yeast expression plasmid pF3A4 was obtained by ligating the fragment with the NotI fragment of about 10.5 kb obtained from vector pAAH5N (Japanese Patent Laid-open Publication No. 2-211880). The artificial fused enzyme consists of 1156 amino acid residues of which sequence structure comprising, successively, from the N-terminal end, an entire amino acid sequence (503 residues) of human liver cytochrome P450 3A4, a linker-derived sequence (Ala-Arg-Ala), and a sequence of from the 42nd residue to C-terminal of yeast NADPH-cytochrome P450 reductase.

Preparation of transformed yeast cell

Saccharomyces cerevisiae AH 22 was inoculated to 1.0 ml of YPD culture medium (1% yeast extract, 2% polypeptone, 2% glucose). After shaken at 30 °C for 18 hours, the yeast cells were collected by centrifugation (5000 x g, 10 min). The resultant cells were suspended in 10 ml of 0.2 M LiCl solution and then centrifuged again (5000 x g, 10 min) to obtain pellets. Then 20 µl of 1 M LiCl solution, 30 µl of 70% polyethylene glycol 4000 and each 10 µl solution containing about 1.0 µg of various kinds of yeast expression plasmids for the human P450 molecular species and yeast NADPH-reductase constructed as above were added to the resultant pellets. After sufficiently mixing them, they were incubated at 30 °C for one hour and further stirred after the addition of 140 µl of sterilized water. The solution was plated on SD synthetic culture medium (2.0% glucose, 0.67% nitrogen base w/o amino acids, manufactured by Difco Co., 20 µg/ml of histidine, 2.0% agar) and incubated at 30 °c for three days. Then transformed yeast cells possessing the yeast expression plasmid described above were selected. In this way, various kinds of yeast cells expressing the human P450 molecular species were prepared.

Quantitative measurement of human P450 expressed in yeast

Each 200 ml of culture broth of each kind of yeast cells expressing human P450 molecular species and yeast NADPH-reductase simultaneously or expressing an artificial fused enzyme comprising human P450 molecular species and yeast NADPH-reductase prepared as above (SD synthetic culture medium, cell concentration: about 1.5 x 10^7 cells/ml) was used to collect the cells. The collected cells were then suspended in 10 ml of 100 mM potassium phosphate buffer solution (pH 7.0) and centrifuged (5000 x g, 10 min) to obtain pellets. Thus obtained pellets were resuspended in 2.0 ml of 100 mM potassium phosphate

buffer solution (pH 7.0) and 1 ml of each of the solutions were poured into two cuvettes. After bubbling carbon monoxide to a sample cuvette, 5 to 10 mg of dithionite was added to both of the cuvettes, and stirred and then difference spectrum at 400-500 nm was measured to calculate the concentration of P450 present in the yeast. The amount of each kind of human P450 species or an artificial fused enzyme in each kind of transformed yeast cells was at a level from about 10^5 to about 10^6 molecules/cell.

Preparation of yeast S-9 Mix fraction, cytoplasmic fraction and microsomal fraction

First, 3.8 liter of each kind of culture broth (SD synthetic culture medium, cell concentration: about 1.0 x 10^8 cells/ml) of yeast cells expressing human P450 molecular species and yeast NADPH-reductase simultaneously or an artificial fused enzyme comprising human P450 molecular species and yeast NADPH-reductase prepared as above was collected and the resultant cells were suspended in 400 ml of a buffer solution A (10 mM Tris-HCl (pH 7.5), 2 M sorbitol, 0.1 mM DTT, 0.2 mM EDTA), to which 160 mg of Zymolyase 100,000 (Zymolyase 100T) was added, and the obtained solution was incubated at 30 • C for 60 min. Spheroplast obtained by centrifugation (5000 x g, 10 min) was suspended in 100 ml of the buffer solution A and then centrifuged (5000 x g, 10 min). Washing the spheroplast by repeating the same centrifugal operation once again, the spheroplast was finally suspended in 200 ml of a buffer solution (10 mM Tris-HCl (pH 7.5), 0.65 M sorbitol, 0.1 mM DTT), which was then subjected to ultrasonic pulverization (50 W, for 5 min). The cell free extracts were centrifuged (9000 x g, 20 min) and supernatants were recovered to obtain a yeast S-9 Mix fraction. Further, the fraction was centrifuged (125,000 x g, 70 min) to collect precipitates which were suspended again into 10 ml of 0.1 M potassium phosphate buffer solution (pH 7.4) to obtain a microsomal fraction. On the other hand, a cytoplasmic fraction was obtained by recovering the supernatants.

Construction of yeast expression plasmid using GAPDH promoter and its expression in yeast

Fig. 18 shows a method of constructing a yeast expression plasmid using a GAPDH promoter. A HindIII fragment (about 3.0 kb) obtained from pARRN (described in the Japanese Patent Laid-open Publication No. 2-211880) was inserted into a HindIII site of plasmid pUN, which was obtained by cleaving pUC19 with EcoRI, blunt-ending and ligation with an NotI linker to give pUR. On the other hand, after blunting an XhoI site of plasmid pAAH5 and inserting an XbaI linker, it was cleaved with restriction enzymes XbaI and SalI and the resultant fragment (about 2.2 kb) was inserted to XbaI and SalI sites of pUC19. The three fragments, namely, a fragment (about 2.2 kb) obtained by cleaving the resultant plasmid with XbaI and PstI, the XbaI-PstI fragment (about 1.3 kb) cut out from 2 μm DNA of Saccharomyces cerevisiae AH22, and a fragment obtained by cleaving pUR with PstI were ligated to give a plasmid pURL. Further, the pURL was cleaved with HindIII, blunted and ligated to remove the HindIII site. Then, an NotI fragment (about 1.6 kb) containing GAPDH promoter and terminator (obtained by the method as described in Agric. Biol. Chem., 51, 1641-1647 (1987) and J. Biol. Chem., 267, 16497-16502 (1992)) was ligated to the NotI site of pURL to give a plasmid pURLG. Human P450 2D6 cDNA obtained by the method used for the construction of p2D6 was inserted to a HindIII site of pURLG to obtain a yeast expression plasmid pG2D6R for simultaneous expression of human P450 2D6 and yeast NADPH-P450 reductase. When the plasmid was introduced by the method used in the preparation of transformed yeast cells as above to Saccharomyces cerevisiae AH22, production of human P450 2D6 was observed.

Metabolism of 7-ethoxycoumarin using transformed yeast cells

7-Ethoxycoumarin was added to each 2 ml of the culture media of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase (SD synthetic culture medium, cell concentration: about 2.0 x 10^7 cells/ml) so that the final concentration of 7-ethoxycoumarin was 0.5 mM. After incubation at 30 • C for 2 or 5 hours, supernatants were obtained by centrifugation (5000 x g, 10 min). To the supernatants 62.5 μl of 15% TCA (trichloroacetic acid) and 2 ml of chloroform were added and, after well stirring, a chloroform layer was recovered by centrifugation (5000 x g, 10 min), to which 4 ml of 0.01 N NaOH containing 0.1 M NaCl was added and stirred sufficiently and then centrifuged (5000 x g, 10 min). After recovering the supernatants, fluorescence was measured for the supernatant fraction (ex. 366 nm, em 452 nm) to quantitatively measure the reaction product 7-hydroxycoumarin. As a result, O-deethylation activity for 7-ethoxycoumarin can be observed for all of 11 kinds of the yeast cells expressing the human P450 molecular species. P450 1A1 and P450 2B6

showed strong activity; and P450 1A2, P450 2E1, P450 2A6 and P450 2D6 showed good activity, while P450 2C8, P450 2C9, P450 3A4, P450 2C18 and P450 2C19 showed moderate activity.

Metabolism of tolbutamide using transformed yeast cells

In the same manner as above, tolbutamide was added to each of the culture solutions of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase so that the concentration of the compound was 1.0 mM. After incubation at 30 • C for 15 hours, the culture supernatant was then obtained by centrifugation (5000 x g, 10 min). To the supernatant, 2 ml of dichloromethane was added. After sufficient stirring, the dichloromethane layer was recovered by centrifugation (5000 x g, 10 min), and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in 100 µl of acetonitrile, and the solution was analyzed by HPLC under the following conditions. As a result, hydroxylated tolbutamide was detected in the solution of yeast cells expressing human P450 2C8, P450 2C9, P450 2C18 and P450 2C19. The human P450 2C9 showed high activity and 2C19 showed good activity. On the other hand, hydroxylated tolbutamide was not detected in the solution of yeast cells expressing other human P450 than described above.

Conditions for HPLC

Column:	µBondapak C18 (manufactured by Waters Co.)
Carrier:	10-70% acetonitrile-distilled water (linear concentration gradient for 20 min)
Temperature:	50 • C
Detection:	UV 230 nm
Injection amount:	50 µl

Metabolism of testosterone using transformed yeast cells

In the same manner as above, testosterone was added to each of the culture solutions of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase so that the concentration of the compound was 0.05 mM. After incubation at 30 • C for 15 hours, the supernatant was obtained by centrifugation (5000 x g, 10 min). Then 2 ml of dichloromethane was added. After sufficient stirring, the solution was centrifuged again (5000 x g, 10 min). The dichloromethane layer was recovered from the separated layer and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in 100 µl of acetonitrile, and the solution was analyzed by HPLC under the following conditions. As a result, hydroxylated testosterone was detected for yeast cells expressing human P450 1A1, P450 2C8 and P450 3A4. On the other hand, hydroxylate testosterone was not detected for yeast cells expressing other human P450 than described above.

Conditions for HPLC

Column:	µBondapak C18 (manufactured by Waters Co.)
Carrier:	20-70% acetonitrile-distilled water (linear concentration gradient for 25 min)
Temperature:	50 • C
Detection:	UV 254 nm
Injection amount:	50 µl

Metabolism of chlorzoxazone using transformed yeast cells and microsomal fractions thereof

Chlorzoxazone was added to each of the culture solutions of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase as above so that the concentration of the compound was 0.5 mM. After incubation at 30 • C for 15 hours, the supernatant was obtained by centrifugation (5000 x g, 10 min). Then 2 ml of dichloromethane was added to the supernatant and vigorously stirred and centrifuged (5000 x g, 10 min). The dichloromethane layer was recovered from the separated layer, then evaporated under reduced pressure. The obtained residue was dissolved in 100 µl of acetonitrile, and the solution was analyzed by HPLC under the following conditions.

NADPH and chlorzoxazone were added to a microsomal fraction of yeasts expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase prepared as above so that the concentrations of NADPDH and chlorzoxazone were 0.5 mM and 250 µM. Then the

solutions were incubated at 37 • C for 10 min. After that, trichloroacetic acid was added to the solutions so that the concentration of the trichloroacetic acid was about 10% (v/v). Then 2 ml of dichloromethane was added to the solution, and the solution was stirred vigorously and centrifuged (15,000 x g, 5 min). The dichloromethane layer was recovered, and the solvent was removed under reduced pressure. The obtained residue was dissolved in 100 µl of acetonitrile and the solution was subjected to analysis by HPLC under the same conditions as above.

All of the yeast cells expressing eleven human P450 molecular species gave hydroxylated chlorzoxazone. P450 2E1 showed high activity, and P450 1A1, P450 1A2, P450 2A6, P450 2D6 showed good activity, while P450 2C8, 2C9, 2B6, 2C18, 2C19 and 3A4 showed moderate activity.

Ames test using yeast S-9 Mix fraction and microsomal fraction

The Ames test method was in accordance with the customary method described, for example, in Mutat. Res., (1975) 31, 347. 2-Aminoanthrathene which is an arylamine type compound was used as a specimen compound. (1) Rat S-9 Mix supernatant fraction (obtained by homogenizing liver and then subjected to centrifugation (9000 x g, 10 min), manufactured by Kikkoman) containing each kind of rat P450 molecular species at the concentration of 1200 pmol per 1 sample and (2) Yeast S-9 Mix fraction obtained from each kind of yeast cells expressing human P450 or a microsomal fraction prepared from the yeast S-9 Mix fraction were used as a metabolic activation source in the Ames test. As a result, more than 1000 revertant colonies were detected for the compound at 1 µg/plate (90 mm dia.) only in the case of using the yeast S-9 Mix fraction obtained from the yeast cells expressing human P450 1A2 (Saccharomyces cerevisiae AH22/p1A2R) and yeast cells expressing human P450 2E1 (Saccharomyces cerevisiae AH22/p2E1R) and a microsomal fraction prepared from the yeast S-9 Mix fraction, while the amounts of the human P450 molecules of these fractions were only one five hundredth and one thirtieth of the human P450 molecules present in the Rat S-9 mixture.

The human cytochrome P450 1A2 showed high activity, and human P450 2E1 showed only moderate activity. But the revertant colonies were not found for the human cytochrome P450 3A4, 2C8 and 2A6.

Metabolism of acetanilide using transformed yeast cells

Acetanilide was added to each of the culture solutions of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase, so that the concentration of the compound was 5 mM, and the solution was incubated at 30 • C for 15 hours. Then the solution was centrifuged (5000 x g, 10 min) to give a supernatant. The obtained supernatant solution was subjected to the HPLC analysis under the following conditions. The hydroxylated acetanilide was found for all of the tested eleven human P450 molecular species.

Among them, P450 1A2 and 2D6 showed high activity and P450 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19 and 2E1 showed good activity, while 3A4 showed moderate activity.

Conditions for HPLC

Column:	µBondapak C18 (manufactured by Waters Co.)
Carrier:	Methanol:water:acetic acid = 15:84:1
Temperature:	30 • C
Detection:	UV 254 nm
Injection amount:	50 µl

Metabolism of coumarin using transformed yeast cells

Coumarin was added to 6 ml of each of the culture solutions (SDS synthetic culture medium, cell concentration of about 2.0 x 10^7 cells/ml) of the transformed yeast cells expressing (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase prepared as above, so that the concentration of the compound was 5 mM, and the solution was incubated at 30 • C for 2 or 5 hours. Then the solution was centrifuged (5000 x g, 10 min) to give a supernatant. 62.5 µl of 15% trichloroacetic acid and 2 ml of chloroform were added to the obtained supernatant solution, and the resultant solution was stirred well. The chloroform layer was recovered from the separated layer. Then 4 ml of sodium hydroxide solution containing 0.1 M NaCl was added to the solution and centrifuged again (5000 x g, 10 min). The supernatant fraction was recovered and subjected to fluorescence analysis (ex. 366 nm, em. 452 nm) to

measure the 7-hydroxycoumarin formed. The hydroxylation activity was specifically found only for the yeast cells expressing the human P450 2A6, while other yeast cells showed no activity.

Metabolism of debrisoquine using the microsomal fraction of transformed yeast whole cells

NADPDH and [^{14}C]debrisoquine were added to each microsomal fraction solution of (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase prepared as above, so that the concentration of the compound was 100 μM and that of NADPH is 6 mM, and the solution was incubated at 30 °C for 30 minutes. Then perchlorate was added to the solution, so that the final concentration of the perchlorate was 10% (v/v). The solution was sufficiently stirred and centrifuged (15,000 x g, 15 min) to give the supernatant. The obtained supernatant was subjected to HPLC analysis according to the following conditions.

Microsomal fractions of yeasts expressing P450 1A1 and 2D6 showed good activity for the hydroxylation of the debrisoquine, while those of yeast cells expressing other human P450 molecular species showed no activity.

Conditions for HPLC

Column: COSMOSIL 5C18 (manufactured by Nakarai Tesq Co.)

Carrier: A(acetonitrile)/B(20mM Sodium Perchlorate, pH = 2.5)

Time (minute)	A/B
0-15	9/91
15-30	9/91-25/75 (linear gradient)
30-32	100/0
32-42	9/91

Temperature: room temperature

Detector: RI ^{14}C

Injection amount: 100 μl

Metabolism of S-mephenytoin using the microsomal fraction of transformed yeast cells

NADPH and [^{14}C]S-mephenytoin were added to each microsomal fraction solution of (i) human cytochrome P450 molecular species and yeast NADPH-P450 reductase; or (ii) an artificial fused enzyme comprising human cytochrome P450 molecular species and yeast NADPH-P450 reductase prepared as above, so that the concentration of the compound was 25 μM and that of NADPH was 3 mM, and the solution was incubated at 30 °C for 30 minutes. Then the solution was diluted with equal volume of methanol, sufficiently stirred and centrifuged (15,000 x g, 5 min) to give the supernatant. The obtained supernatant was subjected to HPLC analysis according to the following conditions.

Microsomal fractions of yeasts expressing P450 2C19 showed good activity for the hydroxylation of the S-mephenytoin, while those of yeast cells expressing other human P450 molecular species showed no activity.

Conditions for HPLC

Column: COSMOSIL 5C18 (manufactured by Nakarai Tesq Co.)

Carrier: A:(Methanol)/(20 mM Potassium phosphate buffer, pH = 7.0) = 40/60
B:Methanol

Time (minute)	A/B
0-18	100/0
18-20	0/100
20-35	100/0

Temperature: room temperature

Detector: RI ^{14}C

Specimen amount: 100 μl

Table 1. Results of the hydroxylation activity using human P450 molecular species

Substrate	Human P450 molecular species										
	1A2	2C9	2E1	3A4	1A1	2A6	2B6	2C8	2C18	2C19	2D6
7-Ethoxycoumarin	++	+	++	+	+++	++	+++	+	+	+	++
Tolbutamide	-	+++	-	-	-	-	-	+	+	++	-
Testosterone	-	-	-	+++	+	-	-	+	-	-	-
Chlorzoxazone	++	+	+++	+	++	++	+	+	+	+	++
2-Aminoanthracene	+++	*	++	-	*	-	*	-	*	*	*
Acetanilide	+++	++	++	+	++	++	++	++	++	++	+++
Coumarin	-	-	-	-	-	+++	-	-	-	-	-
Debrisoquine	-	-	-	-	++	-	-	-	-	-	+++
S-Mephenytoin	-	-	-	-	-	-	-	-	-	+++	-

Hydroxylation activity is designated as follows: +, moderate activity; ++, good activity; +++, high activity; -, no activity; *, not examined.

Metabolism of chlorzoxazone using a mixture of microsomal fractions of transformed yeast cells

Microsomal fractions of yeast expressing cytochrome P450 prepared as above were mixed in the following molar ratios, and the hydroxylation activities of the mixed solutions were measured using

chlorzoxazone.

P450	System A	System B
3A4	35%	33%
2C9	25%	5.8%
2C8		5.8%
2C18		5.8%
2C19		5.8%
1A2	23%	19%
2E1	17%	15%
1A1		2.4%
2A6		3.0%
2B6		2.4%
2D6		2.4%

The substrate, [^{14}C]chlorzoxazone and NADPH were added to the mixed yeast microsomal fractions, so that the concentrations of the compound and NADPH were 382 μM and 3 mM. The solutions were incubated at 37°C for 30 min, and then 1 ml of dichloromethane was added thereto to stop the reaction. After stirring, dichloromethane layer was recovered by centrifugation (10,000 x g, 5 min). Then the solvent was evaporated by the stream of nitrogen gas. The obtained residue was dissolved in 54 μl of acetonitrile and 146 μl of water, the solution was subjected to HPLC analysis under the following conditions.

Conditions for HPLC

Column: COSMOSIL 5C18 (manufactured by Nakarai Tesq Co.)

Carrier: A(Acetonitrile/Water = 27/73)
B(Acetonitrile)

Time (minute)	A/B
0-15	100/0
15-17	0/100
17-25	100/0

Temperature: room temperature

Detector: RI ^{14}C

Injection amount: 100 μl

The metabolites of chlorzoxazone observed by each of the mixed systems A and B were similar to those metabolites which Guengerich reported based on their experimental results by using human liver microsomal fractions (Guengerich, F.P., Chem. Toxicil., Vol.3, pp.566-573, 1990).

Furthermore, the metabolic turnover numbers were calculated for the human liver microsomal fraction (by Guengerich) and for the present yeast microsomal fractions.

The turnover numbers were calculated to be 1.8 and 1.6 in the mixed systems A and B, respectively. The turnover V for the human liver microsomal fraction was calculated using V_{max}, K_m and substrate concentration [S] described in the literature according to the following manner. The results are shown in Table 2. The values somewhat varied due to the difference of individuals, the lowest value being 1.0 and the highest value being 5.9. The values of V for the mixed system B and A fell within this range, both of which were the same level. It was confirmed that the four kinds of molecular species in system A can well reproduce the metabolic system in human liver in vitro.

A turnover V for human cytochrome P450 at an optional substrate concentration can be calculated by substituting V_{max} and K_m described in the literature and substrate concentration [S] of the present example into the Michaelis-Menten's equation:

$$V = (V_{max} * [S])/(K_m + [S])$$

Table 2

Liver sample	Metabolic turnover V [product nmol/nmol P450/min]
#1001	5.9
KDL 14	2.2
KDL 21	1.7
KDL 23	3.0
KDL 27	5.0
H 10	1.1
H 11	1.0
H 12	4.2
H 13	3.3
H 14	2.1
H 15	4.3
H 16	4.0
H 17	3.6
H 18	3.4
Designations of the human liver sample were those used by Guengerich.	

Metabolism of debrisoquine using mixture of microsomal fractions of transformed yeast cells

Microsomal fractions of yeasts expressing human cytochrome P450 were mixed, and the hydroxylation activity of the mixed fraction was measured using debrisoquine. The mixing molar ratio of the human cytochrome P450 molecular species were as follows:

P450	Molar ratio
3A4	33%
2C9	5.8%
2C8	5.8%
2C18	5.8%
2C19	5.8%
1A2	19%
2E1	15%
1A1	2.4%
2B6	2.4%
2D6	2.4%

The substrate debrisoquine and NADPH were added to the mixed microsomal fraction solutions, so that the concentrations were 100 μM for the NADPH and 6 mM for the compound. After the mixture was incubated at 37 °C for 30 min, 50 μl of 60% perchlorate was added to the solution to stop the reaction. The concentration of the perchlorate was finally 12.5% (v/v). After vigorous stirring, the mixture was centrifuged (15,000 x g, 5 min) to recover the supernatant, which was subjected to HPLC analysis under the same conditions used for analyzing the metabolites of debrisoquine.

The metabolites well coincided with the metabolites which Kronbach reported based on the experiments to metabolize the debrisoquine using the human liver microsome (Methods in Enzymology, Vol.206, pp.509-517, 1991).

Metabolism of S-mephenytoin using mixture of microsomal fractions of transformed yeast cells

Microsomal fractions of yeasts expressing various human cytochrome P450 prepared were mixed, and the hydroxylation activity of the mixed fraction was measured for S-mephenytoin. The mixing ratio of the human cytochrome P450 molecular species was the same as that of the mixing system B as described above.

The substrate, [^{14}C]S-mephenytoin and NADPH were added to the mixed microsomal fraction solutions, so that the concentrations were 28 μM for the NADPH and 6 mM for the compound. After the mixture was incubated at 37°C for 30 min, 250 μl of methanol was added to the solution to stop the reaction. After vigorous stirring, the mixture was centrifuged (15,000 x g, 5 min) to recover the supernatant, which was subjected to HPLC analysis under the same conditions used for the hydroxylation of S-mephenytoin using microsomal fraction. The metabolites obtained well coincided with the metabolites which Goldstein reported based on the experiments to metabolize the S-mephenytoin using the human liver microsome (Biochemistry, Vol.33, pp.1743-1752, 1994).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Sumitomo Chemical Company, Limited
(B) STREET: 5-33, Kitahama 4-chome, Chuo-ku,
(C) CITY: Osaka-shi, Osaka-fu
(E) COUNTRY: Japan
(F) POSTAL CODE (ZIP): none

(ii) TITLE OF INVENTION: METHOD FOR SAFETY EVALUATION OF CHEMICAL COMPOUND USING RECOMBINANT YEAST EXPRESSING HUMAN CYTOCHROME P450

(iii) NUMBER OF SEQUENCES: 61

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: JP 201120/1993
(B) FILING DATE: 20-JUL-1993

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: JP 180246/1993
(B) FILING DATE: 21-JUL-1993

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: JP 208279/1993
(B) FILING DATE: 30-JUL-1993

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1551 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1548

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
ATG GCA TTG TCC CAG TCT GTT CCC TTC TCG GCC ACA GAG CTC CTC CTG        48
Met Ala Leu Ser Gln Ser Val Pro Phe Ser Ala Thr Glu Leu Leu Leu
 1               5                  10                  15
```

```
GCC TCT GCC ATC TTC TGC CTG GTA TTC TGG GTG CTC AAG GGT TTG AGG          96
Ala Ser Ala Ile Phe Cys Leu Val Phe Trp Val Leu Lys Gly Leu Arg
                20                  25                  30

CCT CGG GTC CCC AAA GGC CTG AAA AGT CCA CCA GAG CCA TGG GGC TGG         144
Pro Arg Val Pro Lys Gly Leu Lys Ser Pro Pro Glu Pro Trp Gly Trp
            35                  40                  45

CCC TTG CTC GGG CAT GTG CTG ACC CTG GGG AAG AAC CCG CAC CTG GCA         192
Pro Leu Leu Gly His Val Leu Thr Leu Gly Lys Asn Pro His Leu Ala
        50                  55                  60

CTG TCA AGG ATG AGC CAG CGC TAC GGG GAC GTC CTG CAG ATC CGC ATT         240
Leu Ser Arg Met Ser Gln Arg Tyr Gly Asp Val Leu Gln Ile Arg Ile
    65                  70                  75                  80

GGC TCC ACG CCC GTG CTG GTG CTG AGC CGC CTG GAC ACC ATC CGG CAG         288
Gly Ser Thr Pro Val Leu Val Leu Ser Arg Leu Asp Thr Ile Arg Gln
                85                  90                  95

GCC CTG GTG CGG CAG GGC GAC GAT TTC AAG GGC CGG CCT GAC CTC TAC         336
Ala Leu Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr
            100                 105                 110

ACC TCC ACC CTC ATC ACT GAT GGC CAG AGC TTG ACC TTC AGC ACA GAC         384
Thr Ser Thr Leu Ile Thr Asp Gly Gln Ser Leu Thr Phe Ser Thr Asp
        115                 120                 125

TCT GGA CCG GTG TGG GCT GCC CGC CGG CGC CTG GCC CAG AAT GCC CTC         432
Ser Gly Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Ala Leu
    130                 135                 140

AAC ACC TTC TCC ATC GCC TCT GAC CCA GCT TCC TCA TCC TCC TGC TAC         480
Asn Thr Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Ser Ser Cys Tyr
145                 150                 155                 160

CTG GAG GAG CAT GTG AGC AAG GAG GCT AAG GCC CTG ATC AGC AGG TTG         528
Leu Glu Glu His Val Ser Lys Glu Ala Lys Ala Leu Ile Ser Arg Leu
                165                 170                 175

CAG GAG CTG ATG GCA GGG CCT GGG CAC TTC GAC CCT TAC AAT CAG GTG         576
Gln Glu Leu Met Ala Gly Pro Gly His Phe Asp Pro Tyr Asn Gln Val
            180                 185                 190

GTG GTG TCA GTG GCC AAC GTC ATT GGT GCC ATG TGC TTC GGA CAG CAC         624
Val Val Ser Val Ala Asn Val Ile Gly Ala Met Cys Phe Gly Gln His
        195                 200                 205

TTC CCT GAG AGT AGC GAT GAG ATG CTC AGC CTC GTG AAG AAC ACT CAT         672
Phe Pro Glu Ser Ser Asp Glu Met Leu Ser Leu Val Lys Asn Thr His
    210                 215                 220

GAG TTC GTG GAG ACT GCC TCC TCC GGG AAC CCC CTG GAC TTC TTC CCC         720
Glu Phe Val Glu Thr Ala Ser Ser Gly Asn Pro Leu Asp Phe Phe Pro
225                 230                 235                 240

ATC CTT CGC TAC CTG CCT AAC CCT GCC CTG CAG AGG TTC AAG GCC TTC         768
Ile Leu Arg Tyr Leu Pro Asn Pro Ala Leu Gln Arg Phe Lys Ala Phe
                245                 250                 255
```

```
AAC CAG AGG TTC CTG TGG TTC CTG CAG AAA ACA GTC CAG GAG CAC TAT        816
Asn Gln Arg Phe Leu Trp Phe Leu Gln Lys Thr Val Gln Glu His Tyr
            260                 265                 270

CAG GAC TTT GAC AAG AAC AGT GTC CGG GAC ATC ACG GGT GCC CTG TTC        864
Gln Asp Phe Asp Lys Asn Ser Val Arg Asp Ile Thr Gly Ala Leu Phe
        275                 280                 285

AAG CAC AGC AAG AAG GGG CCT AGA GCC AGC GGC AAC CTC ATC CCA CAG        912
Lys His Ser Lys Lys Gly Pro Arg Ala Ser Gly Asn Leu Ile Pro Gln
    290                 295                 300

GAG AAG ATT GTC AAC CTT GTC AAT GAC ATC TTT GGA GCA GGA TTT GAC        960
Glu Lys Ile Val Asn Leu Val Asn Asp Ile Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

ACA GTC ACC ACA GCC ATC TCC TGG AGC CTC ATG TAC CTT GTG ACC AAG       1008
Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Thr Lys
                325                 330                 335

CCT GAG ATA CAG AGG AAG ATC CAG AAG GAG CTG GAC ACT GTG ATT GGC       1056
Pro Glu Ile Gln Arg Lys Ile Gln Lys Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

AGG GAG CGG CGG CCC CGG CTC TCT GAC AGA CCC CAG CTG CCC TAC TTG       1104
Arg Glu Arg Arg Pro Arg Leu Ser Asp Arg Pro Gln Leu Pro Tyr Leu
        355                 360                 365

GAG GCC TTC ATC CTG GAG ACC TTC CGA CAC TCC TCC TTC TTG CCC TTC       1152
Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Leu Pro Phe
    370                 375                 380

ACC ATC CCC CAC AGC ACA ACA AGG GAC ACA ACG CTG AAT GGC TTC TAC       1200
Thr Ile Pro His Ser Thr Thr Arg Asp Thr Thr Leu Asn Gly Phe Tyr
385                 390                 395                 400

ATC CCC AAG AAA TGC TGT GTC TTC GTA AAC CAG TGG CAG GTC AAC CAT       1248
Ile Pro Lys Lys Cys Cys Val Phe Val Asn Gln Trp Gln Val Asn His
                405                 410                 415

GAC CCA GAG CTG TGG GAG GAC CCC TCT GAG TTC CGG CCT GAG CGG TTC       1296
Asp Pro Glu Leu Trp Glu Asp Pro Ser Glu Phe Arg Pro Glu Arg Phe
            420                 425                 430

CTC ACC GCC GAT GGC ACT GCC ATT AAC AAG CCC TTG AGT GAG AAG ATG       1344
Leu Thr Ala Asp Gly Thr Ala Ile Asn Lys Pro Leu Ser Glu Lys Met
        435                 440                 445

ATG CTG TTT GGC ATG GGT AAG CGC CGG TGT ATC GGG GAA GTC CTG GCC       1392
Met Leu Phe Gly Met Gly Lys Arg Arg Cys Ile Gly Glu Val Leu Ala
    450                 455                 460

AAG TGG GAG ATC TTC CTC TTC CTG GCC ATC CTG CTA CAG CAA CTG GAG       1440
Lys Trp Glu Ile Phe Leu Phe Leu Ala Ile Leu Leu Gln Gln Leu Glu
465                 470                 475                 480
```

```
TTC AGC GTG CCG CCG GGC GTG AAA GTC GAC CTG ACC CCC ATC TAC GGG      1488
Phe Ser Val Pro Pro Gly Val Lys Val Asp Leu Thr Pro Ile Tyr Gly
                485                 490                 495

CTG ACC ATG AAG CAC GCC CGC TGT GAA CAT GTC CAG GCG CGG CTG CGC      1536
Leu Thr Met Lys His Ala Arg Cys Glu His Val Gln Ala Arg Leu Arg
            500                 505                 510

TTC TCC ATC AAC TGA                                                  1551
Phe Ser Ile Asn
        515
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 516 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
Met Ala Leu Ser Gln Ser Val Pro Phe Ser Ala Thr Glu Leu Leu Leu
 1               5                  10                  15

Ala Ser Ala Ile Phe Cys Leu Val Phe Trp Val Leu Lys Gly Leu Arg
            20                  25                  30

Pro Arg Val Pro Lys Gly Leu Lys Ser Pro Pro Glu Pro Trp Gly Trp
        35                  40                  45

Pro Leu Leu Gly His Val Leu Thr Leu Gly Lys Asn Pro His Leu Ala
    50                  55                  60

Leu Ser Arg Met Ser Gln Arg Tyr Gly Asp Val Leu Gln Ile Arg Ile
65                  70                  75                  80

Gly Ser Thr Pro Val Leu Val Leu Ser Arg Leu Asp Thr Ile Arg Gln
                85                  90                  95

Ala Leu Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr
            100                 105                 110

Thr Ser Thr Leu Ile Thr Asp Gly Gln Ser Leu Thr Phe Ser Thr Asp
        115                 120                 125

Ser Gly Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Ala Leu
    130                 135                 140

Asn Thr Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Ser Ser Cys Tyr
145                 150                 155                 160

Leu Glu Glu His Val Ser Lys Glu Ala Lys Ala Leu Ile Ser Arg Leu
                165                 170                 175

Gln Glu Leu Met Ala Gly Pro Gly His Phe Asp Pro Tyr Asn Gln Val
            180                 185                 190
```

Val Val Ser Val Ala Asn Val Ile Gly Ala Met Cys Phe Gly Gln His
195 200 205

Phe Pro Glu Ser Ser Asp Glu Met Leu Ser Leu Val Lys Asn Thr His
210 215 220

Glu Phe Val Glu Thr Ala Ser Ser Gly Asn Pro Leu Asp Phe Phe Pro
225 230 235 240

Ile Leu Arg Tyr Leu Pro Asn Pro Ala Leu Gln Arg Phe Lys Ala Phe
245 250 255

Asn Gln Arg Phe Leu Trp Phe Leu Gln Lys Thr Val Gln Glu His Tyr
260 265 270

Gln Asp Phe Asp Lys Asn Ser Val Arg Asp Ile Thr Gly Ala Leu Phe
275 280 285

Lys His Ser Lys Lys Gly Pro Arg Ala Ser Gly Asn Leu Ile Pro Gln
290 295 300

Glu Lys Ile Val Asn Leu Val Asn Asp Ile Phe Gly Ala Gly Phe Asp
305 310 315 320

Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Thr Lys
325 330 335

Pro Glu Ile Gln Arg Lys Ile Gln Lys Glu Leu Asp Thr Val Ile Gly
340 345 350

Arg Glu Arg Arg Pro Arg Leu Ser Asp Arg Pro Gln Leu Pro Tyr Leu
355 360 365

Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Leu Pro Phe
370 375 380

Thr Ile Pro His Ser Thr Thr Arg Asp Thr Thr Leu Asn Gly Phe Tyr
385 390 395 400

Ile Pro Lys Lys Cys Cys Val Phe Val Asn Gln Trp Gln Val Asn His
405 410 415

Asp Pro Glu Leu Trp Glu Asp Pro Ser Glu Phe Arg Pro Glu Arg Phe
420 425 430

Leu Thr Ala Asp Gly Thr Ala Ile Asn Lys Pro Leu Ser Glu Lys Met
435 440 445

Met Leu Phe Gly Met Gly Lys Arg Arg Cys Ile Gly Glu Val Leu Ala
450 455 460

Lys Trp Glu Ile Phe Leu Phe Leu Ala Ile Leu Leu Gln Gln Leu Glu
465 470 475 480

Phe Ser Val Pro Pro Gly Val Lys Val Asp Leu Thr Pro Ile Tyr Gly
485 490 495

```
Leu Thr Met Lys His Ala Arg Cys Glu His Val Gln Ala Arg Leu Arg
            500                 505                 510

Phe Ser Ile Asn
        515
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
ATG GAT TCT ATT GTG TCC CTT GTG CTC TGT CTC TCA TGT TTG CTT CTC        48
Met Asp Ser Ile Val Ser Leu Val Leu Cys Leu Ser Cys Leu Leu Leu
  1               5                  10                  15

CTT TCA CTC TGG AGA CAG AGC TCT GGG AGA GGA AAA CTC CCT CCT GGC        96
Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Lys Leu Pro Pro Gly
            20                  25                  30

CCC ACT CCT CTC CCA GTG ATT GGA AAT ATC CTA CAG ATA GGT ATT AAG       144
Pro Thr Pro Leu Pro Val Ile Gly Asn Ile Leu Gln Ile Gly Ile Lys
        35                  40                  45

GAC ATC AGC AAA TCC TTA ACC AAT CTC TCA AAG GTC TAT GGC CCT GTG       192
Asp Ile Ser Lys Ser Leu Thr Asn Leu Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

TTC ACT CTG TAT TTT GGC CTG AAA CCC ATA GTG GTG CTG CAT GGA TAT       240
Phe Thr Leu Tyr Phe Gly Leu Lys Pro Ile Val Val Leu His Gly Tyr
65                  70                  75                  80

GAA GCA GTG AAG GAA GCC CTG ATT GAT CTT GGA GAG GAG TTT TCT GGA       288
Glu Ala Val Lys Glu Ala Leu Ile Asp Leu Gly Glu Glu Phe Ser Gly
                85                  90                  95

AGA GGC ATT TTC CCA CTG GCT GAA AGA GCT AAC AGA GGA TTT GGA ATT       336
Arg Gly Ile Phe Pro Leu Ala Glu Arg Ala Asn Arg Gly Phe Gly Ile
            100                 105                 110

GTT TTC AGC AAT GGA AAG AAA TGG AAG GAG ATC CGG CGT TTC TCC CTC       384
Val Phe Ser Asn Gly Lys Lys Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

ATG ACG CTG CGG AAT TTT GGG ATG GGG AAG AGG AGC ATT GAG GAC CGT       432
Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140
```

```
GTT CAA GAG GAA GCC CGC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAG        480
Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

GCC TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT        528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCC ATT ATT TTC CAT AAA CGT TTT GAT TAT AAA GAT CAG        576
Val Ile Cys Ser Ile Ile Phe His Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

CAA TTT CTT AAC TTA ATG GAA AAG TTG AAT GAA AAC ATC AAG ATT TTG        624
Gln Phe Leu Asn Leu Met Glu Lys Leu Asn Glu Asn Ile Lys Ile Leu
        195                 200                 205

AGC AGC CCC TGG ATC CAG ATC TGC AAT AAT TTT TCT CCT ATC ATT GAT        672
Ser Ser Pro Trp Ile Gln Ile Cys Asn Asn Phe Ser Pro Ile Ile Asp
    210                 215                 220

TAC TTC CCG GGA ACT CAC AAC AAA TTA CTT AAA AAC GTT GCT TTT ATG        720
Tyr Phe Pro Gly Thr His Asn Lys Leu Leu Lys Asn Val Ala Phe Met
225                 230                 235                 240

AAA AGT TAT ATT TTG GAA AAA GTA AAA GAA CAC CAA GAA TCA ATG GAC        768
Lys Ser Tyr Ile Leu Glu Lys Val Lys Glu His Gln Glu Ser Met Asp
                245                 250                 255

ATG AAC AAC CCT CAG GAC TTT ATT GAT TGC TTC CTG ATG AAA ATG GAG        816
Met Asn Asn Pro Gln Asp Phe Ile Asp Cys Phe Leu Met Lys Met Glu
            260                 265                 270

AAG GAA AAG CAC AAC CAA CCA TCT GAA TTT ACT ATT GAA AGC TTG GAA        864
Lys Glu Lys His Asn Gln Pro Ser Glu Phe Thr Ile Glu Ser Leu Glu
        275                 280                 285

AAC ACT GCA GTT GAC TTG TTT GGA GCT GGG ACA GAG ACG ACA AGC ACA        912
Asn Thr Ala Val Asp Leu Phe Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

ACC CTG AGA TAT GCT CTC CTT CTC CTG CTG AAG CAC CCA GAG GTC ACA        960
Thr Leu Arg Tyr Ala Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAA CGT GTG ATT GGC AGA AAC CGG AGC       1008
Ala Lys Val Gln Glu Glu Ile Glu Arg Val Ile Gly Arg Asn Arg Ser
                325                 330                 335

CCC TGC ATG CAA GAC AGG AGC CAC ATG CCC TAC ACA GAT GCT GTG GTG       1056
Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

CAC GAG GTC CAG AGA TAC ATT GAC CTT CTC CCC ACC AGC CTG CCC CAT       1104
His Glu Val Gln Arg Tyr Ile Asp Leu Leu Pro Thr Ser Leu Pro His
        355                 360                 365

GCA GTG ACC TGT GAC ATT AAA TTC AGA AAC TAT CTC ATT CCC AAG GGC       1152
Ala Val Thr Cys Asp Ile Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380
```

```
ACA ACC ATA TTA ATT TCC CTG ACT TCT GTG CTA CAT GAC AAC AAA GAA      1200
Thr Thr Ile Leu Ile Ser Leu Thr Ser Val Leu His Asp Asn Lys Glu
385                 390                 395                 400

TTT CCC AAC CCA GAG ATG TTT GAC CCT CAT CAC TTT CTG GAT GAA GGT      1248
Phe Pro Asn Pro Glu Met Phe Asp Pro His His Phe Leu Asp Glu Gly
                405                 410                 415

GGC AAT TTT AAG AAA AGT AAA TAC TTC ATG CCT TTC TCA GCA GGA AAA      1296
Gly Asn Phe Lys Lys Ser Lys Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGG ATT TGT GTG GGA GAA GCC CTG GCC GGC ATG GAG CTG TTT TTA TTC      1344
Arg Ile Cys Val Gly Glu Ala Leu Ala Gly Met Glu Leu Phe Leu Phe
        435                 440                 445

CTG ACC TCC ATT TTA CAG AAC TTT AAC CTG AAA TCT CTG GTT GAC CCA      1392
Leu Thr Ser Ile Leu Gln Asn Phe Asn Leu Lys Ser Leu Val Asp Pro
    450                 455                 460

AAG AAC CTT GAC ACC ACT CCA GTT GTC AAT GGA TTT GCC TCT GTG CCG      1440
Lys Asn Leu Asp Thr Thr Pro Val Val Asn Gly Phe Ala Ser Val Pro
465                 470                 475                 480

CCC TTC TAC CAG CTG TGC TTC ATT CCT GTC TGA                         1473
Pro Phe Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Met Asp Ser Ile Val Ser Leu Val Leu Cys Leu Ser Cys Leu Leu Leu
 1               5                  10                  15

Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Lys Leu Pro Pro Gly
            20                  25                  30

Pro Thr Pro Leu Pro Val Ile Gly Asn Ile Leu Gln Ile Gly Ile Lys
        35                  40                  45

Asp Ile Ser Lys Ser Leu Thr Asn Leu Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

Phe Thr Leu Tyr Phe Gly Leu Lys Pro Ile Val Val Leu His Gly Tyr
65                  70                  75                  80

Glu Ala Val Lys Glu Ala Leu Ile Asp Leu Gly Glu Glu Phe Ser Gly
                85                  90                  95
```

```
Arg Gly Ile Phe Pro Leu Ala Glu Arg Ala Asn Arg Gly Phe Gly Ile
            100                 105                 110

Val Phe Ser Asn Gly Lys Lys Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

Val Ile Cys Ser Ile Ile Phe His Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Gln Phe Leu Asn Leu Met Glu Lys Leu Asn Glu Asn Ile Lys Ile Leu
        195                 200                 205

Ser Ser Pro Trp Ile Gln Ile Cys Asn Asn Phe Ser Pro Ile Ile Asp
    210                 215                 220

Tyr Phe Pro Gly Thr His Asn Lys Leu Leu Lys Asn Val Ala Phe Met
225                 230                 235                 240

Lys Ser Tyr Ile Leu Glu Lys Val Lys Glu His Gln Glu Ser Met Asp
                245                 250                 255

Met Asn Asn Pro Gln Asp Phe Ile Asp Cys Phe Leu Met Lys Met Glu
            260                 265                 270

Lys Glu Lys His Asn Gln Pro Ser Glu Phe Thr Ile Glu Ser Leu Glu
        275                 280                 285

Asn Thr Ala Val Asp Leu Phe Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

Thr Leu Arg Tyr Ala Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Glu Arg Val Ile Gly Arg Asn Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Val Gln Arg Tyr Ile Asp Leu Leu Pro Thr Ser Leu Pro His
        355                 360                 365

Ala Val Thr Cys Asp Ile Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Leu Ile Ser Leu Thr Ser Val Leu His Asp Asn Lys Glu
385                 390                 395                 400

Phe Pro Asn Pro Glu Met Phe Asp Pro His His Phe Leu Asp Glu Gly
                405                 410                 415
```

```
Gly Asn Phe Lys Lys Ser Lys Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

Arg Ile Cys Val Gly Glu Ala Leu Ala Gly Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Ser Ile Leu Gln Asn Phe Asn Leu Lys Ser Leu Val Asp Pro
    450                 455                 460

Lys Asn Leu Asp Thr Thr Pro Val Val Asn Gly Phe Ala Ser Val Pro
465                 470                 475                 480

Pro Phe Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1482 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1479

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
ATG TCT GCC CTC GGA GTC ACC GTG GCC CTG CTG GTG TGG GCG GCC TTC        48
Met Ser Ala Leu Gly Val Thr Val Ala Leu Leu Val Trp Ala Ala Phe
 1               5                  10                  15

CTC CTG CTG GTG TCC ATG TGG AGG CAG GTG CAC AGC AGC TGG AAT CTG        96
Leu Leu Leu Val Ser Met Trp Arg Gln Val His Ser Ser Trp Asn Leu
            20                  25                  30

CCC CCA GGC CCT TTC CCG CTT CCC ATC ATC GGG AAC CTC TTC CAG TTG       144
Pro Pro Gly Pro Phe Pro Leu Pro Ile Ile Gly Asn Leu Phe Gln Leu
        35                  40                  45

GAA TTG AAG AAT ATT CCC AAG TCC TTC ACC CGG TTG GCC CAG CGC TTC       192
Glu Leu Lys Asn Ile Pro Lys Ser Phe Thr Arg Leu Ala Gln Arg Phe
    50                  55                  60

GGG CCG GTG TTC ACG CTG TAC GTG GGC TCG CAG CGC ATG GTG GTG ATG       240
Gly Pro Val Phe Thr Leu Tyr Val Gly Ser Gln Arg Met Val Val Met
65                  70                  75                  80

CAC GGC TAC AAG GCG GTG AAG GAA GCG CTG CTG GAC TAC AAG GAC GAG       288
His Gly Tyr Lys Ala Val Lys Glu Ala Leu Leu Asp Tyr Lys Asp Glu
                85                  90                  95

TTC TCG GGC AGA GGC GAC CTC CCC GCG TTC CAT GCG CAC AGG GAC AGG       336
Phe Ser Gly Arg Gly Asp Leu Pro Ala Phe His Ala His Arg Asp Arg
            100                 105                 110
```

```
GGA ATC ATT TTT AAT AAT GGA CCT ACC TGG AAG GAC ATC CGG CGG TTT      384
Gly Ile Ile Phe Asn Asn Gly Pro Thr Trp Lys Asp Ile Arg Arg Phe
        115                 120                 125

TCC CTG ACC ACC CTC CGG AAC TAT GGG ATG GGG AAA CAG GGC AAT GAG      432
Ser Leu Thr Thr Leu Arg Asn Tyr Gly Met Gly Lys Gln Gly Asn Glu
    130                 135                 140

AGC CGG ATC CAG AGG GAG GCC CAC TTC CTG CTG GAA GCA CTC AGG AAG      480
Ser Arg Ile Gln Arg Glu Ala His Phe Leu Leu Glu Ala Leu Arg Lys
145                 150                 155                 160

ACC CAA GGC CAG CCT TTC GAC CCC ACC TTC CTC ATC GGG TGC GCG CCC      528
Thr Gln Gly Gln Pro Phe Asp Pro Thr Phe Leu Ile Gly Cys Ala Pro
                165                 170                 175

TGC AAC GTC ATA GCC GAC ATC CTC TTC CGC AAG CAT TTT GAC TAC AAT      576
Cys Asn Val Ile Ala Asp Ile Leu Phe Arg Lys His Phe Asp Tyr Asn
            180                 185                 190

GAT GAG AAG TTT CTA AGG CTG ATG TAT TTG TTT AAT GAG AAC TTC CAC      624
Asp Glu Lys Phe Leu Arg Leu Met Tyr Leu Phe Asn Glu Asn Phe His
        195                 200                 205

CTA CTC AGC ACT CCC TGG CTC CAG CTT TAC AAT AAT TTT CCC AGC TTT      672
Leu Leu Ser Thr Pro Trp Leu Gln Leu Tyr Asn Asn Phe Pro Ser Phe
    210                 215                 220

CTA CAC TAC TTG CCT GGA AGC CAC AGA AAA GTC ATA AAA AAT GTG GCT      720
Leu His Tyr Leu Pro Gly Ser His Arg Lys Val Ile Lys Asn Val Ala
225                 230                 235                 240

GAA GTA AAA GAG TAT GTG TCT GAA AGG GTG AAG GAG CAC CAT CAA TCT      768
Glu Val Lys Glu Tyr Val Ser Glu Arg Val Lys Glu His His Gln Ser
                245                 250                 255

CTG GAC CCC AAC TGT CCC CGG GAC CTC ACC GAC TGC CTG CTC GTG GAA      816
Leu Asp Pro Asn Cys Pro Arg Asp Leu Thr Asp Cys Leu Leu Val Glu
            260                 265                 270

ATG GAG AAG GAA AAG CAC AGT GCA GAG CGC TTG TAC ACA ATG GAC GGT      864
Met Glu Lys Glu Lys His Ser Ala Glu Arg Leu Tyr Thr Met Asp Gly
        275                 280                 285

ATC ACC GTG ACT GTG GCC GAC CTG TTC TTT GCG GGG ACA GAG ACC ACC      912
Ile Thr Val Thr Val Ala Asp Leu Phe Phe Ala Gly Thr Glu Thr Thr
    290                 295                 300

AGC ACA ACT CTG AGA TAT GGG CTC CTG ATT CTC ATG AAA TAC CCT GAG      960
Ser Thr Thr Leu Arg Tyr Gly Leu Leu Ile Leu Met Lys Tyr Pro Glu
305                 310                 315                 320

ATC GAA GAG AAG CTC CAT GAA GAA ATT GAC AGG GTG ATT GGG CCA AGC     1008
Ile Glu Glu Lys Leu His Glu Glu Ile Asp Arg Val Ile Gly Pro Ser
                325                 330                 335
```

```
CGA ATC CCT GCC ATC AAG GAT AGG CAA GAG ATG CCC TAC ATG GAT GCT      1056
Arg Ile Pro Ala Ile Lys Asp Arg Gln Glu Met Pro Tyr Met Asp Ala
            340                 345                 350

GTG GTG CAT GAG ATT CAG CGG TTC ATC ACC CTC GTG CCC TCC AAC CTG      1104
Val Val His Glu Ile Gln Arg Phe Ile Thr Leu Val Pro Ser Asn Leu
        355                 360                 365

CCC CAT GAA GCA ACC CGA GAC ACC ATT TTC AGA GGA TAC CTC ATC CCC      1152
Pro His Glu Ala Thr Arg Asp Thr Ile Phe Arg Gly Tyr Leu Ile Pro
    370                 375                 380

AAG GGC ACA GTC GTA GTG CCA ACT CTG GAC TCT GTT TTG TAT GAC AAC      1200
Lys Gly Thr Val Val Val Pro Thr Leu Asp Ser Val Leu Tyr Asp Asn
385                 390                 395                 400

CAA GAA TTT CCT GAT CCA GAA AAG TTT AAG CCA GAA CAC TTC CTG AAT      1248
Gln Glu Phe Pro Asp Pro Glu Lys Phe Lys Pro Glu His Phe Leu Asn
                405                 410                 415

GAA AAT GGA AAG TTC AAG TAC AGT GAC TAT TTC AAG CCA TTT TCC ACA      1296
Glu Asn Gly Lys Phe Lys Tyr Ser Asp Tyr Phe Lys Pro Phe Ser Thr
            420                 425                 430

GGA AAA CGA GTG TGT GCT GGA GAA GGC CTG GCT CGC ATG GAG TTG TTT      1344
Gly Lys Arg Val Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe
        435                 440                 445

CTT TTG TTG TGT GCC ATT TTG CAG CAT TTT AAT TTG AAG CCT CTC GTT      1392
Leu Leu Leu Cys Ala Ile Leu Gln His Phe Asn Leu Lys Pro Leu Val
    450                 455                 460

GAC CCA AAG GAT ATC GAC CTC AGC CCT ATA CAT ATT GGG TTT GGC TGT      1440
Asp Pro Lys Asp Ile Asp Leu Ser Pro Ile His Ile Gly Phe Gly Cys
465                 470                 475                 480

ATC CCA CCA CGT TAC AAA CTC TGT GTC ATT CCC CGC TCA TGA              1482
Ile Pro Pro Arg Tyr Lys Leu Cys Val Ile Pro Arg Ser
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 493 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

```
Met Ser Ala Leu Gly Val Thr Val Ala Leu Leu Val Trp Ala Ala Phe
 1               5                  10                  15

Leu Leu Leu Val Ser Met Trp Arg Gln Val His Ser Ser Trp Asn Leu
            20                  25                  30
```

```
Pro Pro Gly Pro Phe Pro Leu Pro Ile Ile Gly Asn Leu Phe Gln Leu
        35                  40                  45

Glu Leu Lys Asn Ile Pro Lys Ser Phe Thr Arg Leu Ala Gln Arg Phe
    50                  55                  60

Gly Pro Val Phe Thr Leu Tyr Val Gly Ser Gln Arg Met Val Val Met
65                  70                  75                  80

His Gly Tyr Lys Ala Val Lys Glu Ala Leu Leu Asp Tyr Lys Asp Glu
                85                  90                  95

Phe Ser Gly Arg Gly Asp Leu Pro Ala Phe His Ala His Arg Asp Arg
            100                 105                 110

Gly Ile Ile Phe Asn Asn Gly Pro Thr Trp Lys Asp Ile Arg Arg Phe
        115                 120                 125

Ser Leu Thr Thr Leu Arg Asn Tyr Gly Met Gly Lys Gln Gly Asn Glu
    130                 135                 140

Ser Arg Ile Gln Arg Glu Ala His Phe Leu Leu Glu Ala Leu Arg Lys
145                 150                 155                 160

Thr Gln Gly Gln Pro Phe Asp Pro Thr Phe Leu Ile Gly Cys Ala Pro
                165                 170                 175

Cys Asn Val Ile Ala Asp Ile Leu Phe Arg Lys His Phe Asp Tyr Asn
            180                 185                 190

Asp Glu Lys Phe Leu Arg Leu Met Tyr Leu Phe Asn Glu Asn Phe His
        195                 200                 205

Leu Leu Ser Thr Pro Trp Leu Gln Leu Tyr Asn Asn Phe Pro Ser Phe
    210                 215                 220

Leu His Tyr Leu Pro Gly Ser His Arg Lys Val Ile Lys Asn Val Ala
225                 230                 235                 240

Glu Val Lys Glu Tyr Val Ser Glu Arg Val Lys Glu His His Gln Ser
                245                 250                 255

Leu Asp Pro Asn Cys Pro Arg Asp Leu Thr Asp Cys Leu Leu Val Glu
            260                 265                 270

Met Glu Lys Glu Lys His Ser Ala Glu Arg Leu Tyr Thr Met Asp Gly
        275                 280                 285

Ile Thr Val Thr Val Ala Asp Leu Phe Phe Ala Gly Thr Glu Thr Thr
    290                 295                 300

Ser Thr Thr Leu Arg Tyr Gly Leu Leu Ile Leu Met Lys Tyr Pro Glu
305                 310                 315                 320

Ile Glu Glu Lys Leu His Glu Glu Ile Asp Arg Val Ile Gly Pro Ser
                325                 330                 335

Arg Ile Pro Ala Ile Lys Asp Arg Gln Glu Met Pro Tyr Met Asp Ala
            340                 345                 350
```

```
Val Val His Glu Ile Gln Arg Phe Ile Thr Leu Val Pro Ser Asn Leu
        355                 360                 365

Pro His Glu Ala Thr Arg Asp Thr Ile Phe Arg Gly Tyr Leu Ile Pro
    370                 375                 380

Lys Gly Thr Val Val Val Pro Thr Leu Asp Ser Val Leu Tyr Asp Asn
385                 390                 395                 400

Gln Glu Phe Pro Asp Pro Glu Lys Phe Lys Pro Glu His Phe Leu Asn
                405                 410                 415

Glu Asn Gly Lys Phe Lys Tyr Ser Asp Tyr Phe Lys Pro Phe Ser Thr
            420                 425                 430

Gly Lys Arg Val Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe
        435                 440                 445

Leu Leu Leu Cys Ala Ile Leu Gln His Phe Asn Leu Lys Pro Leu Val
    450                 455                 460

Asp Pro Lys Asp Ile Asp Leu Ser Pro Ile His Ile Gly Phe Gly Cys
465                 470                 475                 480

Ile Pro Pro Arg Tyr Lys Leu Cys Val Ile Pro Arg Ser
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1509

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
ATG GCT CTC ATC CCA GAC TTG GCC ATG GAA ACC TGG CTT CTC CTG GCT        48
Met Ala Leu Ile Pro Asp Leu Ala Met Glu Thr Trp Leu Leu Leu Ala
  1               5                  10                  15

GTC AGC CTG GTG CTC CTC TAT CTA TAT GGA ACC CAT TCA CAT GGA CTT        96
Val Ser Leu Val Leu Leu Tyr Leu Tyr Gly Thr His Ser His Gly Leu
            20                  25                  30

TTT AAG AAG CTT GGA ATT CCA GGG CCC ACA CCT CTG CCT TTT TTG GGA       144
Phe Lys Lys Leu Gly Ile Pro Gly Pro Thr Pro Leu Pro Phe Leu Gly
        35                  40                  45

AAT ATT TTG TCC TAC CAT AAG GGC TTT TGT ATG TTT GAC ATG GAA TGT       192
Asn Ile Leu Ser Tyr His Lys Gly Phe Cys Met Phe Asp Met Glu Cys
    50                  55                  60
```

```
CAT AAA AAG TAT GGA AAA GTG TGG GGC TTT TAT GAT GGT CAA CAG CCT        240
His Lys Lys Tyr Gly Lys Val Trp Gly Phe Tyr Asp Gly Gln Gln Pro
 65                  70                  75                  80

GTG CTG GCT ATC ACA GAT CCT GAC ATG ATC AAA ACA GTG CTA GTG AAA        288
Val Leu Ala Ile Thr Asp Pro Asp Met Ile Lys Thr Val Leu Val Lys
                85                  90                  95

GAA TGT TAT TCT GTC TTC ACA AAC CGG AGG CCT TTT GGT CCA GTG GGA        336
Glu Cys Tyr Ser Val Phe Thr Asn Arg Arg Pro Phe Gly Pro Val Gly
            100                 105                 110

TTT ATG AAA AGT GCC ATC TCT ATA GCT GAG GAT GAA GAA TGG AAG AGA        384
Phe Met Lys Ser Ala Ile Ser Ile Ala Glu Asp Glu Glu Trp Lys Arg
        115                 120                 125

TTA CGA TCA TTG CTG TCT CCA ACC TTC ACC AGT GGA AAA CTC AAG GAG        432
Leu Arg Ser Leu Leu Ser Pro Thr Phe Thr Ser Gly Lys Leu Lys Glu
    130                 135                 140

ATG GTC CCT ATC ATT GCC CAG TAT GGA GAT GTG TTG GTG AGA AAT CTG        480
Met Val Pro Ile Ile Ala Gln Tyr Gly Asp Val Leu Val Arg Asn Leu
145                 150                 155                 160

AGG CGG GAA GCA GAG ACA GGC AAG CCT GTC ACC TTG AAA GAC GTC TTT        528
Arg Arg Glu Ala Glu Thr Gly Lys Pro Val Thr Leu Lys Asp Val Phe
                165                 170                 175

GGG GCC TAC AGC ATG GAT GTG ATC ACT AGC ACA TCA TTT GGA GTG AAC        576
Gly Ala Tyr Ser Met Asp Val Ile Thr Ser Thr Ser Phe Gly Val Asn
            180                 185                 190

ATC GAC TCT CTC AAC AAT CCA CAA GAC CCC TTT GTG GAA AAC ACC AAG        624
Ile Asp Ser Leu Asn Asn Pro Gln Asp Pro Phe Val Glu Asn Thr Lys
        195                 200                 205

AAG CTT TTA AGA TTT GAT TTT TTG GAT CCA TTC TTT CTC TCA ATA ACA        672
Lys Leu Leu Arg Phe Asp Phe Leu Asp Pro Phe Phe Leu Ser Ile Thr
    210                 215                 220

GTC TTT CCA TTC CTC ATC CCA ATT CTT GAA GTA TTA AAT ATC TGT GTG        720
Val Phe Pro Phe Leu Ile Pro Ile Leu Glu Val Leu Asn Ile Cys Val
225                 230                 235                 240

TTT CCA AGA GAA GTT ACA AAT TTT TTA AGA AAA TCT GTA AAA AGG ATG        768
Phe Pro Arg Glu Val Thr Asn Phe Leu Arg Lys Ser Val Lys Arg Met
                245                 250                 255

AAA GAA AGT CGC CTC GAA GAT ACA CAA AAG CAC CGA GTG GAT TTC CTT        816
Lys Glu Ser Arg Leu Glu Asp Thr Gln Lys His Arg Val Asp Phe Leu
            260                 265                 270

CAG CTG ATG ATT GAC TCT CAG AAT TCA AAA GAA ACT GAG TCC CAC AAA        864
Gln Leu Met Ile Asp Ser Gln Asn Ser Lys Glu Thr Glu Ser His Lys
        275                 280                 285
```

```
GCT CTG TCC GAT CTG GAG CTC GTG GCC CAA TCA ATT ATC TTT ATT TTT        912
Ala Leu Ser Asp Leu Glu Leu Val Ala Gln Ser Ile Ile Phe Ile Phe
    290                 295                 300

GCT GGC TAT GAA ACC ACG AGC AGT GTT CTC TCC TTC ATT ATG TAT GAA        960
Ala Gly Tyr Glu Thr Thr Ser Ser Val Leu Ser Phe Ile Met Tyr Glu
305                 310                 315                 320

CTG GCC ACT CAC CCT GAT GTC CAG CAG AAA CTG CAG GAG GAA ATT GAT       1008
Leu Ala Thr His Pro Asp Val Gln Gln Lys Leu Gln Glu Glu Ile Asp
                325                 330                 335

GCA GTT TTA CCC AAT AAG GCA CCA CCC ACC TAT GAT ACT GTG CTA CAG       1056
Ala Val Leu Pro Asn Lys Ala Pro Pro Thr Tyr Asp Thr Val Leu Gln
            340                 345                 350

ATG GAG TAT CTT GAC ATG GTG GTG AAT GAA ACG CTC AGA TTA TTC CCA       1104
Met Glu Tyr Leu Asp Met Val Val Asn Glu Thr Leu Arg Leu Phe Pro
        355                 360                 365

ATT GCT ATG AGA CTT GAG AGG GTC TGC AAA AAA GAT GTT GAG ATC AAT       1152
Ile Ala Met Arg Leu Glu Arg Val Cys Lys Lys Asp Val Glu Ile Asn
    370                 375                 380

GGG ATG TTC ATT CCC AAA GGG TGG GTG GTG ATG ATT CCA AGC TAT GCT       1200
Gly Met Phe Ile Pro Lys Gly Trp Val Val Met Ile Pro Ser Tyr Ala
385                 390                 395                 400

CTT CAC CGT GAC CCA AAG TAC TGG ACA GAG CCT GAG AAG TTC CTC CCT       1248
Leu His Arg Asp Pro Lys Tyr Trp Thr Glu Pro Glu Lys Phe Leu Pro
                405                 410                 415

GAA AGA TTC AGC AAG AAG AAC AAG GAC AAC ATA GAT CCT TAC ATA TAC       1296
Glu Arg Phe Ser Lys Lys Asn Lys Asp Asn Ile Asp Pro Tyr Ile Tyr
            420                 425                 430

ACA CCC TTT GGA AGT GGA CCC AGA AAC TGC ATT GGC ATG AGG TTT GCT       1344
Thr Pro Phe Gly Ser Gly Pro Arg Asn Cys Ile Gly Met Arg Phe Ala
        435                 440                 445

CTC ATG AAC ATG AAA CTT GCT CTA ATC AGA GTC CTT CAG AAC TTC TCC       1392
Leu Met Asn Met Lys Leu Ala Leu Ile Arg Val Leu Gln Asn Phe Ser
    450                 455                 460

TTC AAA CCT TGT AAA GAA ACA CAG ATC CCC CTG AAA TTA AGC TTA GGA       1440
Phe Lys Pro Cys Lys Glu Thr Gln Ile Pro Leu Lys Leu Ser Leu Gly
465                 470                 475                 480

GGA CTT CTT CAA CCA GAA AAA CCC GTT GTT CTA AAG GTT GAG TCA AGG       1488
Gly Leu Leu Gln Pro Glu Lys Pro Val Val Leu Lys Val Glu Ser Arg
                485                 490                 495

GAT GGC ACC GTA AGT GGA GCC TGA                                      1512
Asp Gly Thr Val Ser Gly Ala
            500
```

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 503 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

```
Met Ala Leu Ile Pro Asp Leu Ala Met Glu Thr Trp Leu Leu Leu Ala
 1               5                  10                  15

Val Ser Leu Val Leu Leu Tyr Leu Tyr Gly Thr His Ser His Gly Leu
            20                  25                  30

Phe Lys Lys Leu Gly Ile Pro Gly Pro Thr Pro Leu Pro Phe Leu Gly
        35                  40                  45

Asn Ile Leu Ser Tyr His Lys Gly Phe Cys Met Phe Asp Met Glu Cys
    50                  55                  60

His Lys Lys Tyr Gly Lys Val Trp Gly Phe Tyr Asp Gly Gln Gln Pro
65                  70                  75                  80

Val Leu Ala Ile Thr Asp Pro Asp Met Ile Lys Thr Val Leu Val Lys
                85                  90                  95

Glu Cys Tyr Ser Val Phe Thr Asn Arg Arg Pro Phe Gly Pro Val Gly
            100                 105                 110

Phe Met Lys Ser Ala Ile Ser Ile Ala Glu Asp Glu Glu Trp Lys Arg
        115                 120                 125

Leu Arg Ser Leu Leu Ser Pro Thr Phe Thr Ser Gly Lys Leu Lys Glu
    130                 135                 140

Met Val Pro Ile Ile Ala Gln Tyr Gly Asp Val Leu Val Arg Asn Leu
145                 150                 155                 160

Arg Arg Glu Ala Glu Thr Gly Lys Pro Val Thr Leu Lys Asp Val Phe
                165                 170                 175

Gly Ala Tyr Ser Met Asp Val Ile Thr Ser Thr Ser Phe Gly Val Asn
            180                 185                 190

Ile Asp Ser Leu Asn Asn Pro Gln Asp Pro Phe Val Glu Asn Thr Lys
        195                 200                 205

Lys Leu Leu Arg Phe Asp Phe Leu Asp Pro Phe Phe Leu Ser Ile Thr
    210                 215                 220

Val Phe Pro Phe Leu Ile Pro Ile Leu Glu Val Leu Asn Ile Cys Val
225                 230                 235                 240

Phe Pro Arg Glu Val Thr Asn Phe Leu Arg Lys Ser Val Lys Arg Met
                245                 250                 255
```

```
Lys Glu Ser Arg Leu Glu Asp Thr Gln Lys His Arg Val Asp Phe Leu
            260                 265                 270

Gln Leu Met Ile Asp Ser Gln Asn Ser Lys Glu Thr Glu Ser His Lys
        275                 280                 285

Ala Leu Ser Asp Leu Glu Leu Val Ala Gln Ser Ile Ile Phe Ile Phe
    290                 295                 300

Ala Gly Tyr Glu Thr Thr Ser Ser Val Leu Ser Phe Ile Met Tyr Glu
305                 310                 315                 320

Leu Ala Thr His Pro Asp Val Gln Gln Lys Leu Gln Glu Glu Ile Asp
                325                 330                 335

Ala Val Leu Pro Asn Lys Ala Pro Pro Thr Tyr Asp Thr Val Leu Gln
            340                 345                 350

Met Glu Tyr Leu Asp Met Val Val Asn Glu Thr Leu Arg Leu Phe Pro
        355                 360                 365

Ile Ala Met Arg Leu Glu Arg Val Cys Lys Lys Asp Val Glu Ile Asn
    370                 375                 380

Gly Met Phe Ile Pro Lys Gly Trp Val Val Met Ile Pro Ser Tyr Ala
385                 390                 395                 400

Leu His Arg Asp Pro Lys Tyr Trp Thr Glu Pro Glu Lys Phe Leu Pro
                405                 410                 415

Glu Arg Phe Ser Lys Lys Asn Lys Asp Asn Ile Asp Pro Tyr Ile Tyr
            420                 425                 430

Thr Pro Phe Gly Ser Gly Pro Arg Asn Cys Ile Gly Met Arg Phe Ala
        435                 440                 445

Leu Met Asn Met Lys Leu Ala Leu Ile Arg Val Leu Gln Asn Phe Ser
    450                 455                 460

Phe Lys Pro Cys Lys Glu Thr Gln Ile Pro Leu Lys Leu Ser Leu Gly
465                 470                 475                 480

Gly Leu Leu Gln Pro Glu Lys Pro Val Val Leu Lys Val Glu Ser Arg
                485                 490                 495

Asp Gly Thr Val Ser Gly Ala
            500
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1539 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1536

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
ATG CTT TTC CCA ATC TCC ATG TCG GCC ACG GAG TTT CTT CTG GCC TCT        48
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
  1               5                  10                  15

GTC ATC TTC TGT CTG GTA TTC TGG GTA ATC AGG GCC TCA AGA CCT CAG        96
Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

GTC CCC AAA GGC CTG AAG AAT CCA CCA GGG CCA TGG GGC TGG CCT CTG       144
Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45

ATT GGG CAC ATG CTG ACC CTG GGA AAG AAC CCG CAC CTG GCA CTG TCA       192
Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
    50                  55                  60

AGG ATG AGC CAG CAG TAT GGG GAC GTG CTG CAG ATC CGA ATT GGC TCC       240
Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
65                  70                  75                  80

ACA CCC GTG GTG GTG CTG AGC GGC CTG GAC ACC ATC CGG CAG GCC CTG       288
Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                85                  90                  95

GTG CGG CAG GGC GAT GAT TTC AAG GGC CGG CCC GAC CTC TAC ACC TTC       336
Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

ACC CTC ATC AGT AAT GGT CAG AGC ATG TCC TTC AGC CCA GAC TCT GGA       384
Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125

CCA GTG TGG GCT GCC CGC CGG CGC CTG GCC CAG AAT GGC CTG AAA AGT       432
Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140

TTC TCC ATT GCC TCT GAC CCA GCC TCC TCA ACC TCC TGC TAC CTG GAA       480
Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

GAG CAT GTG AGC AAG GAG GCT GAG GTC CTG ATA AGC ACG TTG CAG GAG       528
Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

CTG ATG GCA GGG CCT GGG CAC TTT AAC CCC TAC AGG TAT GTG GTG GTA       576
Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

TCA GTG ACC AAT GTC ATC TGT GCC ATT TGC TTT GGC CGG CGC TAT GAC       624
Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205
```

```
CAC AAC CAC CAA GAA CTG CTT AGC CTA GTC AAC CTG AAT AAT AAT TTC        672
His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

GGG GAG GTG GTT GGC TCT GGA AAC CCA GCT GAC TTC ATC CCT ATT CTT        720
Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

CGC TAC CTA CCC AAC CCT TCC CTG AAT GCC TTC AAG GAC CTG AAT GAG        768
Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255

AAG TTC TAC AGC TTC ATG CAG AAG ATG GTC AAG GAG CAC TAC AAA ACC        816
Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

TTT GAG AAG GGC CAC ATC CGG GAC ATC ACA GAC AGC CTG ATT GAG CAC        864
Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285

TGT CAG GAG AAG CAG CTG GAT GAG AAC GCC AAT GTC CAG CTG TCA GAT        912
Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

GAG AAG ATC ATT AAC ATC GTC TTG GAC CTC TTT GGA GCT GGG TTT GAC        960
Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

ACA GTC ACA ACT GCT ATC TCC TGG AGC CTC ATG TAT TTG GTG ATG AAC       1008
Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

CCC AGG GTA CAG AGA AAG ATC CAA GAG GAG CTC GAC ACA GTG ATT GGC       1056
Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

AGG TCA CGG CGG CCC CGG CTC TCT GAC AGA TCC CAT CTG CCC TAT ATG       1104
Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365

GAG GCC TTC ATC CTG GAG ACC TTC CGA CAC TCT TCC TTC GTC CCC TTC       1152
Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

ACC ATC CCC CAC AGC ACA ACA AGA GAC ACA AGT TTG AAA GGC TTT TAC       1200
Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

ATC CCC AAG GGG CGT TGT GTC TTT GTA AAC CAG TGG CAG ATC AAC CAT       1248
Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

GAC CAG AAG CTA TGG GTC AAC CCA TCT GAG TTC CTA CCT GAA CGG TTT       1296
Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

CTC ACC CCT GAT GGT GCT ATC GAC AAG GTG TTA AGT GAG AAG GTG ATT       1344
Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445
```

```
ATC TTT GGC ATG GGC AAG CGG AAG TGT ATC GGT GAG ACC ATT GCC AGC      1392
Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Ile Ala Ser
    450                 455                 460

TGG GAG GTC TTT CTC TTC CTG GCT ATC CTG CTG CAA CGG GTG GAA TTC      1440
Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

AGC GTG CCA CTG GGC GTG AAG GTG GAC ATG ACC CCC ATC TAT GGG CTA      1488
Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

ACC ATG AAG CAT GCC TGC TGT GAG CAC TTC CAA ATG CAG CTG CGC TCT      1536
Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510

TAG                                                                 1539
```

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

```
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
  1               5                  10                  15

Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45

Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
    50                  55                  60

Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
65                  70                  75                  80

Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                85                  90                  95

Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125

Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140
```

```
Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205

His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255

Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285

Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365

Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445

Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Ile Ala Ser
    450                 455                 460
```

```
Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510
```

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1539 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1536

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

```
ATG CTT TTC CCA ATC TCC ATG TCG GCC ACG GAG TTT CTT CTG GCC TCT        48
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
 1               5                  10                  15

GTC ATC TTC TGT CTG GTA TTC TGG GTA ATC AGG GCC TCA AGA CCT CAG        96
Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

GTC CCC AAA GGC CTG AAG AAT CCA CCA GGG CCA TGG GGC TGG CCT CTG       144
Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45

ATT GGG CAC ATG CTG ACC CTG GGA AAG AAC CCG CAC CTG GCA CTG TCA       192
Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
    50                  55                  60

AGG ATG AGC CAG CAG TAT GGG GAC GTG CTG CAG ATC CGA ATT GGC TCC       240
Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
65                  70                  75                  80

ACA CCC GTG GTG GTG CTG AGC GGC CTG GAC ACC ATC CGG CAG GCC CTG       288
Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                85                  90                  95

GTG CGG CAG GGC GAT GAT TTC AAG GGC CGG CCC GAC CTC TAC ACC TTC       336
Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

ACC CTC ATC AGT AAT GGT CAG AGC ATG TCC TTC AGC CCA GAC TCT GGA       384
Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125
```

```
CCA GTG TGG GCT GCC CGC CGG CGC CTG GCC CAG AAT GGC CTG AAA AGT      432
Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140

TTC TCC ATT GCC TCT GAC CCA GCC TCC TCA ACC TCC TGC TAC CTG GAA      480
Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

GAG CAT GTG AGC AAG GAG GCT GAG GTC CTG ATA AGC ACG TTG CAG GAG      528
Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

CTG ATG GCA GGG CCT GGG CAC TTT AAC CCC TAC AGG TAT GTG GTG GTA      576
Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

TCA GTG ACC AAT GTC ATC TGT GCC ATT TGC TTT GGC CGG CGC TAT GAC      624
Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205

CAC AAC CAC CAA GAA CTG CTT AGC CTA GTC AAC CTG AAT AAT AAT TTC      672
His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

GGG GAG GTG GTT GGC TCT GGA AAC CCA GCT GAC TTC ATC CCT ATT CTT      720
Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

CGC TAC CTA CCC AAC CCT TCC CTG AAT GCC TTC AAG GAC CTG AAT GAG      768
Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255

AAG TTC TAC AGC TTC ATG CAG AAG ATG GTC AAG GAG CAC TAC AAA ACC      816
Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

TTT GAG AAG GGC CAC ATC CGG GAC ATC ACA GAC AGC CTG ATT GAG CAC      864
Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285

TGT CAG GAG AAG CAG CTG GAT GAG AAC GCC AAT GTC CAG CTG TCA GAT      912
Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

GAG AAG ATC ATT AAC ATC GTC TTG GAC CTC TTT GGA GCT GGG TTT GAC      960
Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

ACA GTC ACA ACT GCT ATC TCC TGG AGC CTC ATG TAT TTG GTG ATG AAC     1008
Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

CCC AGG GTA CAG AGA AAG ATC CAA GAG GAG CTC GAC ACA GTG ATT GGC     1056
Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

AGG TCA CGG CGG CCC CGG CTC TCT GAC AGA TCC CAT CTG CCC TAT ATG     1104
Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365
```

```
GAG GCC TTC ATC CTG GAG ACC TTC CGA CAC TCT TCC TTC GTC CCC TTC      1152
Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

ACC ATC CCC CAC AGC ACA ACA AGA GAC ACA AGT TTG AAA GGC TTT TAC      1200
Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

ATC CCC AAG GGG CGT TGT GTC TTT GTA AAC CAG TGG CAG ATC AAC CAT      1248
Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

GAC CAG AAG CTA TGG GTC AAC CCA TCT GAG TTC CTA CCT GAA CGG TTT      1296
Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

CTC ACC CCT GAT GGT GCT ATC GAC AAG GTG TTA AGT GAG AAG GTG ATT      1344
Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445

ATC TTT GGC ATG GGC AAG CGG AAG TGT ATC GGT GAG ACC ATT GCC CGC      1392
Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Ile Ala Arg
    450                 455                 460

TGG GAG GTC TTT CTC TTC CTG GCT ATC CTG CTG CAA CGG GTG GAA TTC      1440
Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

AGC GTG CCA CTG GGC GTG AAG GTG GAC ATG ACC CCC ATC TAT GGG CTA      1488
Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

ACC ATG AAG CAT GCC TGC TGT GAG CAC TTC CAA ATG CAG CTG CGC TCT      1536
Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510

TAG                                                                 1539
```

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

```
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
  1               5                  10                  15

Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45
```

```
Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
 50                  55                  60

Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
65                  70                  75                  80

Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                85                  90                  95

Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125

Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140

Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205

His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255

Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285

Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350
```

```
Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365

Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445

Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Ile Ala Arg
    450                 455                 460

Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510
```

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1539 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1536

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

```
ATG CTT TTC CCA ATC TCC ATG TCG GCC ACG GAG TTT CTT CTG GCC TCT        48
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
  1               5                  10                  15

GTC ATC TTC TGT CTG GTA TTC TGG GTA ATC AGG GCC TCA AGA CCT CAG        96
Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

GTC CCC AAA GGC CTG AAG AAT CCA CCA GGG CCA TGG GGC TGG CCT CTG       144
Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45
```

```
ATT GGG CAC ATG CTG ACC CTG GGA AAG AAC CCG CAC CTG GCA CTG TCA        192
Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
     50                  55                  60

AGG ATG AGC CAG CAG TAT GGG GAC GTG CTG CAG ATC CGA ATT GGC TCC        240
Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
 65                  70                  75                  80

ACA CCC GTG GTG GTG CTG AGC GGC CTG GAC ACC ATC CGG CAG GCC CTG        288
Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                 85                  90                  95

GTG CGG CAG GGC GAT GAT TTC AAG GGC CGG CCC GAC CTC TAC ACC TTC        336
Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

ACC CTC ATC AGT AAT GGT CAG AGC ATG TCC TTC AGC CCA GAC TCT GGA        384
Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125

CCA GTG TGG GCT GCC CGC CGG CGC CTG GCC CAG AAT GGC CTG AAA AGT        432
Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140

TTC TCC ATT GCC TCT GAC CCA GCC TCC TCA ACC TCC TGC TAC CTG GAA        480
Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

GAG CAT GTG AGC AAG GAG GCT GAG GTC CTG ATA AGC ACG TTG CAG GAG        528
Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

CTG ATG GCA GGG CCT GGG CAC TTT AAC CCC TAC AGG TAT GTG GTG GTA        576
Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

TCA GTG ACC AAT GTC ATC TGT GCC ATT TGC TTT GGC CGG CGC TAT GAC        624
Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205

CAC AAC CAC CAA GAA CTG CTT AGC CTA GTC AAC CTG AAT AAT AAT TTC        672
His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

GGG GAG GTG GTT GGC TCT GGA AAC CCA GCT GAC TTC ATC CCT ATT CTT        720
Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

CGC TAC CTA CCC AAC CCT TCC CTG AAT GCC TTC AAG GAC CTG AAT GAG        768
Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255

AAG TTC TAC AGC TTC ATG CAG AAG ATG GTC AAG GAG CAC TAC AAA ACC        816
Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

TTT GAG AAG GGC CAC ATC CGG GAC ATC ACA GAC AGC CTG ATT GAG CAC        864
Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285
```

```
TGT CAG GAG AAG CAG CTG GAT GAG AAC GCC AAT GTC CAG CTG TCA GAT        912
Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

GAG AAG ATC ATT AAC ATC GTC TTG GAC CTC TTT GGA GCT GGG TTT GAC        960
Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

ACA GTC ACA ACT GCT ATC TCC TGG AGC CTC ATG TAT TTG GTG ATG AAC       1008
Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

CCC AGG GTA CAG AGA AAG ATC CAA GAG GAG CTC GAC ACA GTG ATT GGC       1056
Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

AGG TCA CGG CGG CCC CGG CTC TCT GAC AGA TCC CAT CTG CCC TAT ATG       1104
Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365

GAG GCC TTC ATC CTG GAG ACC TTC CGA CAC TCT TCC TTC GTC CCC TTC       1152
Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

ACC ATC CCC CAC AGC ACA ACA AGA GAC ACA AGT TTG AAA GGC TTT TAC       1200
Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

ATC CCC AAG GGG CGT TGT GTC TTT GTA AAC CAG TGG CAG ATC AAC CAT       1248
Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

GAC CAG AAG CTA TGG GTC AAC CCA TCT GAG TTC CTA CCT GAA CGG TTT       1296
Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

CTC ACC CCT GAT GGT GCT ATC GAC AAG GTG TTA AGT GAG AAG GTG ATT       1344
Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445

ATC TTT GGC ATG GGC AAG CGG AAG TGT ATC GGT GAG ACC GTT GCC CGC       1392
Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Val Ala Arg
    450                 455                 460

TGG GAG GTC TTT CTC TTC CTG GCT ATC CTG CTG CAA CGG GTG GAA TTC       1440
Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

AGC GTG CCA CTG GGC GTG AAG GTG GAC ATG ACC CCC ATC TAT GGG CTA       1488
Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

ACC ATG AAG CAT GCC TGC TGT GAG CAC TTC CAA ATG CAG CTG CGC TCT       1536
Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510

TAG                                                                  1539
```

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
Met Leu Phe Pro Ile Ser Met Ser Ala Thr Glu Phe Leu Leu Ala Ser
 1               5                  10                  15

Val Ile Phe Cys Leu Val Phe Trp Val Ile Arg Ala Ser Arg Pro Gln
            20                  25                  30

Val Pro Lys Gly Leu Lys Asn Pro Pro Gly Pro Trp Gly Trp Pro Leu
        35                  40                  45

Ile Gly His Met Leu Thr Leu Gly Lys Asn Pro His Leu Ala Leu Ser
    50                  55                  60

Arg Met Ser Gln Gln Tyr Gly Asp Val Leu Gln Ile Arg Ile Gly Ser
65                  70                  75                  80

Thr Pro Val Val Val Leu Ser Gly Leu Asp Thr Ile Arg Gln Ala Leu
                85                  90                  95

Val Arg Gln Gly Asp Asp Phe Lys Gly Arg Pro Asp Leu Tyr Thr Phe
            100                 105                 110

Thr Leu Ile Ser Asn Gly Gln Ser Met Ser Phe Ser Pro Asp Ser Gly
        115                 120                 125

Pro Val Trp Ala Ala Arg Arg Arg Leu Ala Gln Asn Gly Leu Lys Ser
    130                 135                 140

Phe Ser Ile Ala Ser Asp Pro Ala Ser Ser Thr Ser Cys Tyr Leu Glu
145                 150                 155                 160

Glu His Val Ser Lys Glu Ala Glu Val Leu Ile Ser Thr Leu Gln Glu
                165                 170                 175

Leu Met Ala Gly Pro Gly His Phe Asn Pro Tyr Arg Tyr Val Val Val
            180                 185                 190

Ser Val Thr Asn Val Ile Cys Ala Ile Cys Phe Gly Arg Arg Tyr Asp
        195                 200                 205

His Asn His Gln Glu Leu Leu Ser Leu Val Asn Leu Asn Asn Asn Phe
    210                 215                 220

Gly Glu Val Val Gly Ser Gly Asn Pro Ala Asp Phe Ile Pro Ile Leu
225                 230                 235                 240

Arg Tyr Leu Pro Asn Pro Ser Leu Asn Ala Phe Lys Asp Leu Asn Glu
                245                 250                 255
```

```
Lys Phe Tyr Ser Phe Met Gln Lys Met Val Lys Glu His Tyr Lys Thr
            260                 265                 270

Phe Glu Lys Gly His Ile Arg Asp Ile Thr Asp Ser Leu Ile Glu His
        275                 280                 285

Cys Gln Glu Lys Gln Leu Asp Glu Asn Ala Asn Val Gln Leu Ser Asp
    290                 295                 300

Glu Lys Ile Ile Asn Ile Val Leu Asp Leu Phe Gly Ala Gly Phe Asp
305                 310                 315                 320

Thr Val Thr Thr Ala Ile Ser Trp Ser Leu Met Tyr Leu Val Met Asn
                325                 330                 335

Pro Arg Val Gln Arg Lys Ile Gln Glu Glu Leu Asp Thr Val Ile Gly
            340                 345                 350

Arg Ser Arg Arg Pro Arg Leu Ser Asp Arg Ser His Leu Pro Tyr Met
        355                 360                 365

Glu Ala Phe Ile Leu Glu Thr Phe Arg His Ser Ser Phe Val Pro Phe
    370                 375                 380

Thr Ile Pro His Ser Thr Thr Arg Asp Thr Ser Leu Lys Gly Phe Tyr
385                 390                 395                 400

Ile Pro Lys Gly Arg Cys Val Phe Val Asn Gln Trp Gln Ile Asn His
                405                 410                 415

Asp Gln Lys Leu Trp Val Asn Pro Ser Glu Phe Leu Pro Glu Arg Phe
            420                 425                 430

Leu Thr Pro Asp Gly Ala Ile Asp Lys Val Leu Ser Glu Lys Val Ile
        435                 440                 445

Ile Phe Gly Met Gly Lys Arg Lys Cys Ile Gly Glu Thr Val Ala Arg
    450                 455                 460

Trp Glu Val Phe Leu Phe Leu Ala Ile Leu Leu Gln Arg Val Glu Phe
465                 470                 475                 480

Ser Val Pro Leu Gly Val Lys Val Asp Met Thr Pro Ile Tyr Gly Leu
                485                 490                 495

Thr Met Lys His Ala Cys Cys Glu His Phe Gln Met Gln Leu Arg Ser
            500                 505                 510
```

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1485 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1482

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

```
ATG CTG GCC TCA GGG ATG CTT CTG GTG GCC TTG CTG GTC TGC CTG ACT   48
Met Leu Ala Ser Gly Met Leu Leu Val Ala Leu Leu Val Cys Leu Thr
  1               5                  10                  15

GTG ATG GTC TTG ATG TCT GTT TGG CAG CAG AGG AAG AGC AAG GGG AAG   96
Val Met Val Leu Met Ser Val Trp Gln Gln Arg Lys Ser Lys Gly Lys
            20                  25                  30

CTG CCT CCG GGA CCC ACC CCA TTG CCC TTC ATT GGA AAC TAC CTG CAG  144
Leu Pro Pro Gly Pro Thr Pro Leu Pro Phe Ile Gly Asn Tyr Leu Gln
        35                  40                  45

CTG AAC ACA GAG CAG ATG TAC AAC TCC CTC ATG AAG ATC AGT GAG CGC  192
Leu Asn Thr Glu Gln Met Tyr Asn Ser Leu Met Lys Ile Ser Glu Arg
    50                  55                  60

TAT GGC CCC GTG TTC ACC ATT CAC TTG GGG CCC CGG CGG GTC GTG GTG  240
Tyr Gly Pro Val Phe Thr Ile His Leu Gly Pro Arg Arg Val Val Val
65                  70                  75                  80

CTG TGT GGA CAT GAT GCC GTC AGG GAG GCT CTG GTG GAC CAG GCT GAG  288
Leu Cys Gly His Asp Ala Val Arg Glu Ala Leu Val Asp Gln Ala Glu
                85                  90                  95

GAG TTC AGC GGG CGA GGC GAG CAA GCC ACC TTC GAC TGG GTC TTC AAA  336
Glu Phe Ser Gly Arg Gly Glu Gln Ala Thr Phe Asp Trp Val Phe Lys
            100                 105                 110

GGC TAT GGC GTG GTA TTC AGC AAC GGG GAG CGC GCC AAG CAG CTC CGG  384
Gly Tyr Gly Val Val Phe Ser Asn Gly Glu Arg Ala Lys Gln Leu Arg
        115                 120                 125

CGC TTC TCC ATC GCC ACC CTG CGG GAC TTC GGG GTG GGC AAG CGA GGC  432
Arg Phe Ser Ile Ala Thr Leu Arg Asp Phe Gly Val Gly Lys Arg Gly
    130                 135                 140

ATC GAG GAG CGC ATC CAG GAG GAG GCG GGC TTC CTC ATC GAC GCC CTC  480
Ile Glu Glu Arg Ile Gln Glu Glu Ala Gly Phe Leu Ile Asp Ala Leu
145                 150                 155                 160

CGG GGC ACT GGC GGC GCC AAT ATC GAT CCC ACC TTC TTC CTG AGC CGC  528
Arg Gly Thr Gly Gly Ala Asn Ile Asp Pro Thr Phe Phe Leu Ser Arg
                165                 170                 175

ACA GTC TCC AAT GTC ATC AGC TCC ATT GTC TTT GGG GAC CGC TTT GAC  576
Thr Val Ser Asn Val Ile Ser Ser Ile Val Phe Gly Asp Arg Phe Asp
            180                 185                 190

TAT AAG GAC AAA GAG TTC CTG TCA CTG TTG CGC ATG ATG CTA GGA ATC  624
Tyr Lys Asp Lys Glu Phe Leu Ser Leu Leu Arg Met Met Leu Gly Ile
        195                 200                 205
```

```
TTC CAG TTC ACG TCA ACC TCC ACG GGG CAG CTC TAT GAG ATG TTC TCT        672
Phe Gln Phe Thr Ser Thr Ser Thr Gly Gln Leu Tyr Glu Met Phe Ser
    210                 215                 220

TCG GTG ATG AAA CAC CTG CCA GGA CCA CAG CAA CAG GCC TTT CAG TTG        720
Ser Val Met Lys His Leu Pro Gly Pro Gln Gln Gln Ala Phe Gln Leu
225                 230                 235                 240

CTG CAA GGG CTG GAG GAC TTC ATA GCC AAG AAG GTG GAG CAC AAC CAG        768
Leu Gln Gly Leu Glu Asp Phe Ile Ala Lys Lys Val Glu His Asn Gln
                245                 250                 255

CGC ACG CTG GAT CCC AAT TCC CCA CGG GAC TTC ATT GAC TCC TTT CTC        816
Arg Thr Leu Asp Pro Asn Ser Pro Arg Asp Phe Ile Asp Ser Phe Leu
            260                 265                 270

ATC CGC ATG CAG GAG GAG GAG AAG AAC CCC AAC ACG GAG TTC TAC TTG        864
Ile Arg Met Gln Glu Glu Glu Lys Asn Pro Asn Thr Glu Phe Tyr Leu
        275                 280                 285

AAA AAC CTG GTG ATG ACC ACG TTG AAC CTC TTC ATT GGG GGC ACC GAG        912
Lys Asn Leu Val Met Thr Thr Leu Asn Leu Phe Ile Gly Gly Thr Glu
    290                 295                 300

ACC GTC AGC ACC ACC CTG CGC TAT GGC TTC TTG CTG CTC ATG AAG CAC        960
Thr Val Ser Thr Thr Leu Arg Tyr Gly Phe Leu Leu Leu Met Lys His
305                 310                 315                 320

CCA GAG GTG GAG GCC AAG GTC CAT GAG GAG ATT GAC AGA GTG ATC GGC       1008
Pro Glu Val Glu Ala Lys Val His Glu Glu Ile Asp Arg Val Ile Gly
                325                 330                 335

AAG AAC CGG CAG CCC AAG TTT GAG GAC CGG GCC AAG ATG CCC TAC ATG       1056
Lys Asn Arg Gln Pro Lys Phe Glu Asp Arg Ala Lys Met Pro Tyr Met
            340                 345                 350

GAG GCA GTG ATC CAC GAG ATC CAA AGA TTT GGA GAC GTG ATC CCC ATG       1104
Glu Ala Val Ile His Glu Ile Gln Arg Phe Gly Asp Val Ile Pro Met
        355                 360                 365

AGT TTG GCC CGC AGA GTC AAA AAG GAC ACC AAG TTT CGG GAT TTC TTC       1152
Ser Leu Ala Arg Arg Val Lys Lys Asp Thr Lys Phe Arg Asp Phe Phe
    370                 375                 380

CTC CCT AAG GGC ACC GAA GTG TAC CCT ATG CTG GGC TCT GTG CTG AGA       1200
Leu Pro Lys Gly Thr Glu Val Tyr Pro Met Leu Gly Ser Val Leu Arg
385                 390                 395                 400

GAC CCC AGT TTC TTC TCC AAC CCC CAG GAC TTC AAT CCC CAG CAC TTC       1248
Asp Pro Ser Phe Phe Ser Asn Pro Gln Asp Phe Asn Pro Gln His Phe
                405                 410                 415

CTG AAT GAG AAG GGG CAG TTT AAG AAG AGT GAT GCT TTT GTG CCC TTT       1296
Leu Asn Glu Lys Gly Gln Phe Lys Lys Ser Asp Ala Phe Val Pro Phe
            420                 425                 430

TCC ATC GGA AAG CGG AAC TGT TTC GGA GAA GGC CTG GCC AGA ATG GAG       1344
Ser Ile Gly Lys Arg Asn Cys Phe Gly Glu Gly Leu Ala Arg Met Glu
        435                 440                 445
```

```
CTC TTT CTC TTC TTC ACC ACC GTC ATG CAG AAC TTC CGC CTC AAG TCC      1392
Leu Phe Leu Phe Phe Thr Thr Val Met Gln Asn Phe Arg Leu Lys Ser
    450                 455                 460

TCC CAG TCA CCT AAG GAC ATT GAC GTG TCC CCC AGA CAC GTG GGC TTT      1440
Ser Gln Ser Pro Lys Asp Ile Asp Val Ser Pro Arg His Val Gly Phe
465                 470                 475                 480

GCC ACG ATC CCA CGA AAC TAC ACC ATG AGC TTC CTG CCC CGC              1482
Ala Thr Ile Pro Arg Asn Tyr Thr Met Ser Phe Leu Pro Arg
                485                 490

TGA                                                                  1485
```

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 494 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

```
Met Leu Ala Ser Gly Met Leu Leu Val Ala Leu Leu Val Cys Leu Thr
 1               5                  10                  15

Val Met Val Leu Met Ser Val Trp Gln Gln Arg Lys Ser Lys Gly Lys
            20                  25                  30

Leu Pro Pro Gly Pro Thr Pro Leu Pro Phe Ile Gly Asn Tyr Leu Gln
        35                  40                  45

Leu Asn Thr Glu Gln Met Tyr Asn Ser Leu Met Lys Ile Ser Glu Arg
    50                  55                  60

Tyr Gly Pro Val Phe Thr Ile His Leu Gly Pro Arg Arg Val Val Val
65                  70                  75                  80

Leu Cys Gly His Asp Ala Val Arg Glu Ala Leu Val Asp Gln Ala Glu
                85                  90                  95

Glu Phe Ser Gly Arg Gly Glu Gln Ala Thr Phe Asp Trp Val Phe Lys
            100                 105                 110

Gly Tyr Gly Val Val Phe Ser Asn Gly Glu Arg Ala Lys Gln Leu Arg
        115                 120                 125

Arg Phe Ser Ile Ala Thr Leu Arg Asp Phe Gly Val Gly Lys Arg Gly
    130                 135                 140

Ile Glu Glu Arg Ile Gln Glu Glu Ala Gly Phe Leu Ile Asp Ala Leu
145                 150                 155                 160

Arg Gly Thr Gly Gly Ala Asn Ile Asp Pro Thr Phe Phe Leu Ser Arg
                165                 170                 175
```

```
Thr Val Ser Asn Val Ile Ser Ser Ile Val Phe Gly Asp Arg Phe Asp
            180                 185                 190

Tyr Lys Asp Lys Glu Phe Leu Ser Leu Leu Arg Met Met Leu Gly Ile
        195                 200                 205

Phe Gln Phe Thr Ser Thr Ser Thr Gly Gln Leu Tyr Glu Met Phe Ser
    210                 215                 220

Ser Val Met Lys His Leu Pro Gly Pro Gln Gln Gln Ala Phe Gln Leu
225                 230                 235                 240

Leu Gln Gly Leu Glu Asp Phe Ile Ala Lys Lys Val Glu His Asn Gln
                245                 250                 255

Arg Thr Leu Asp Pro Asn Ser Pro Arg Asp Phe Ile Asp Ser Phe Leu
            260                 265                 270

Ile Arg Met Gln Glu Glu Glu Lys Asn Pro Asn Thr Glu Phe Tyr Leu
        275                 280                 285

Lys Asn Leu Val Met Thr Thr Leu Asn Leu Phe Ile Gly Gly Thr Glu
    290                 295                 300

Thr Val Ser Thr Thr Leu Arg Tyr Gly Phe Leu Leu Leu Met Lys His
305                 310                 315                 320

Pro Glu Val Glu Ala Lys Val His Glu Glu Ile Asp Arg Val Ile Gly
                325                 330                 335

Lys Asn Arg Gln Pro Lys Phe Glu Asp Arg Ala Lys Met Pro Tyr Met
            340                 345                 350

Glu Ala Val Ile His Glu Ile Gln Arg Phe Gly Asp Val Ile Pro Met
        355                 360                 365

Ser Leu Ala Arg Arg Val Lys Lys Asp Thr Lys Phe Arg Asp Phe Phe
    370                 375                 380

Leu Pro Lys Gly Thr Glu Val Tyr Pro Met Leu Gly Ser Val Leu Arg
385                 390                 395                 400

Asp Pro Ser Phe Phe Ser Asn Pro Gln Asp Phe Asn Pro Gln His Phe
                405                 410                 415

Leu Asn Glu Lys Gly Gln Phe Lys Lys Ser Asp Ala Phe Val Pro Phe
            420                 425                 430

Ser Ile Gly Lys Arg Asn Cys Phe Gly Glu Gly Leu Ala Arg Met Glu
        435                 440                 445

Leu Phe Leu Phe Phe Thr Thr Val Met Gln Asn Phe Arg Leu Lys Ser
    450                 455                 460

Ser Gln Ser Pro Lys Asp Ile Asp Val Ser Pro Arg His Val Gly Phe
465                 470                 475                 480
```

```
Ala Thr Ile Pro Arg Asn Tyr Thr Met Ser Phe Leu Pro Arg
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1485 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1482

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

```
ATG CTG GCC TCA GGG ATG CTT CTG GTG GCC TTG CTG GTC TGC CTG ACT        48
Met Leu Ala Ser Gly Met Leu Leu Val Ala Leu Leu Val Cys Leu Thr
  1               5                  10                  15

GTG ATG GTC TTG ATG TCT GTT TGG CAG CAG AGG AAG AGC AAG GGG AAG        96
Val Met Val Leu Met Ser Val Trp Gln Gln Arg Lys Ser Lys Gly Lys
            20                  25                  30

CTG CCT CCG GGA CCC ACC CCA TTG CCC TTC ATT GGA AAC TAC CTG CAG       144
Leu Pro Pro Gly Pro Thr Pro Leu Pro Phe Ile Gly Asn Tyr Leu Gln
        35                  40                  45

CTG AAC ACA GAG CAG ATG TAC AAC TCC CTC ATG AAG ATC AGT GAG CGC       192
Leu Asn Thr Glu Gln Met Tyr Asn Ser Leu Met Lys Ile Ser Glu Arg
    50                  55                  60

TAT GGC CCC GTG TTC ACC ATT CAC TTG GGG CCC CGG CGG GTC GTG GTG       240
Tyr Gly Pro Val Phe Thr Ile His Leu Gly Pro Arg Arg Val Val Val
65                  70                  75                  80

CTG TGT GGA CAT GAT GCC GTC AGG GAG GCT CTG GTG GAC CAG GCT GAG       288
Leu Cys Gly His Asp Ala Val Arg Glu Ala Leu Val Asp Gln Ala Glu
                85                  90                  95

GAG TTC AGC GGG CGA GGC GAG CAA GCC ACC TTC GAC TGG GTC TTC AAA       336
Glu Phe Ser Gly Arg Gly Glu Gln Ala Thr Phe Asp Trp Val Phe Lys
            100                 105                 110

GGC TAT GGC GTG GTA TTC AGC AAC GGG GAG CGC GCC AAG CAG CTC CGG       384
Gly Tyr Gly Val Val Phe Ser Asn Gly Glu Arg Ala Lys Gln Leu Arg
        115                 120                 125

CGC TTC TCC ATC GCC ACC CTG CGG GAC TTC GGG GTG GGC AAG CGA GGC       432
Arg Phe Ser Ile Ala Thr Leu Arg Asp Phe Gly Val Gly Lys Arg Gly
    130                 135                 140

ATC GAG GAG CGC ATC CAG GAG GAG GCG GGC TTC CTC ATC GAC GCC CTC       480
Ile Glu Glu Arg Ile Gln Glu Glu Ala Gly Phe Leu Ile Asp Ala Leu
145                 150                 155                 160
```

```
CGG GGC ACT GGC GGC GCC AAT ATC GAT CCC ACC TTC TTC CTG AGC CGC      528
Arg Gly Thr Gly Gly Ala Asn Ile Asp Pro Thr Phe Phe Leu Ser Arg
                165                 170                 175

ACA GTC TCC AAT GTC ATC AGC TCC ATT GTC TTT GGG GAC CGC TTT GAC      576
Thr Val Ser Asn Val Ile Ser Ser Ile Val Phe Gly Asp Arg Phe Asp
            180                 185                 190

TAT AAG GAC AAA GAG TTC CTG TCA CTG TTG CGC ATG ATG CTA GGA ATC      624
Tyr Lys Asp Lys Glu Phe Leu Ser Leu Leu Arg Met Met Leu Gly Ile
        195                 200                 205

TTC CAG TTC ACG TCA ACC TCC ACG GGG CAG CTC TAT GAG ATG TTC TCT      672
Phe Gln Phe Thr Ser Thr Ser Thr Gly Gln Leu Tyr Glu Met Phe Ser
    210                 215                 220

TCG GTG ATG AAA CAC CTG CCA GGA CCA CAG CAA CAG GCC TTT CAG TTG      720
Ser Val Met Lys His Leu Pro Gly Pro Gln Gln Gln Ala Phe Gln Leu
225                 230                 235                 240

CTG CAA GGG CTG GAG GAC TTC ATA GCC AAG AAG GTG GAG CAC AAC CAG      768
Leu Gln Gly Leu Glu Asp Phe Ile Ala Lys Lys Val Glu His Asn Gln
                245                 250                 255

CGC ACG CTG GAT CCC AAT TCC CCA CGG GAC TTC ATT GAC TCC TTT CTC      816
Arg Thr Leu Asp Pro Asn Ser Pro Arg Asp Phe Ile Asp Ser Phe Leu
            260                 265                 270

ATC CGC ATG CAG GAG GAG GAG AAG AAC CCC AAC ACG GAG TTC TAC TTG      864
Ile Arg Met Gln Glu Glu Glu Lys Asn Pro Asn Thr Glu Phe Tyr Leu
        275                 280                 285

AAA AAC CTG GTG ATG ACC ACG TTG AAC CTC TTC ATT GGG GGC ACC GAG      912
Lys Asn Leu Val Met Thr Thr Leu Asn Leu Phe Ile Gly Gly Thr Glu
    290                 295                 300

ACC GTC AGC ACC ACC CTG CGC TAT GGC TTC TTG CTG CTC ATG AAG CAC      960
Thr Val Ser Thr Thr Leu Arg Tyr Gly Phe Leu Leu Leu Met Lys His
305                 310                 315                 320

CCA GAG GTG GAG GCC AAG GTC CAT GAG GAG ATT GAC AGA GTG ATC GGC     1008
Pro Glu Val Glu Ala Lys Val His Glu Glu Ile Asp Arg Val Ile Gly
                325                 330                 335

AAG AAC CGG CAG CCC AAG TTT GAG GAC CGG GCC AAG ATG CCC TAC ATG     1056
Lys Asn Arg Gln Pro Lys Phe Glu Asp Arg Ala Lys Met Pro Tyr Met
            340                 345                 350

GAG GCA GTG ATC CAC GAG ATC CAA AGA TTT GGA GAC GTG ATC CCC ATG     1104
Glu Ala Val Ile His Glu Ile Gln Arg Phe Gly Asp Val Ile Pro Met
        355                 360                 365

AGT TTG GCC CGC AGA GTC AAA AAG GAC ACC AAG TTT CGG GAT TTC TTC     1152
Ser Leu Ala Arg Arg Val Lys Lys Asp Thr Lys Phe Arg Asp Phe Phe
    370                 375                 380

CTC CCT AAG GGC ACC GAA GTG TAC CCT ATG CTG GGC TCT GTG CTG AGA     1200
Leu Pro Lys Gly Thr Glu Val Tyr Pro Met Leu Gly Ser Val Leu Arg
385                 390                 395                 400
```

```
GAC CCC AGT TTC TTC TCC AAC CCC CAG GAC TTC AAT CCC CAG CAC TTC      1248
Asp Pro Ser Phe Phe Ser Asn Pro Gln Asp Phe Asn Pro Gln His Phe
                405                 410                 415

CTG AAT GAG AAG GGG CAG TTT AAG AAG AGT GAT GCT TTT GTG CCC TTT      1296
Leu Asn Glu Lys Gly Gln Phe Lys Lys Ser Asp Ala Phe Val Pro Phe
            420                 425                 430

TCC ATC GGA AAG CGG AAC TGT TTC GGA GAA GGC CTG GCC AGA ATG GAG      1344
Ser Ile Gly Lys Arg Asn Cys Phe Gly Glu Gly Leu Ala Arg Met Glu
        435                 440                 445

CTC TTT CTC TTC TTC ACC ACC GTC ATG CAG AAC TTC CGC CTC AAG TCC      1392
Leu Phe Leu Phe Phe Thr Thr Val Met Gln Asn Phe Arg Leu Lys Ser
    450                 455                 460

TCC CAG TCA CCT AAG GAC ATT GAC GTG TCC CCC AAA CAC GTG GGC TTT      1440
Ser Gln Ser Pro Lys Asp Ile Asp Val Ser Pro Lys His Val Gly Phe
465                 470                 475                 480

GCC ACG ATC CCA CGA AAC TAC ACC ATG AGC TTC CTG CCC CGC              1482
Ala Thr Ile Pro Arg Asn Tyr Thr Met Ser Phe Leu Pro Arg
                485                 490

TGA                                                                 1485
```

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 494 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

```
Met Leu Ala Ser Gly Met Leu Leu Val Ala Leu Leu Val Cys Leu Thr
 1               5                  10                  15

Val Met Val Leu Met Ser Val Trp Gln Gln Arg Lys Ser Lys Gly Lys
            20                  25                  30

Leu Pro Pro Gly Pro Thr Pro Leu Pro Phe Ile Gly Asn Tyr Leu Gln
        35                  40                  45

Leu Asn Thr Glu Gln Met Tyr Asn Ser Leu Met Lys Ile Ser Glu Arg
    50                  55                  60

Tyr Gly Pro Val Phe Thr Ile His Leu Gly Pro Arg Arg Val Val Val
65                  70                  75                  80

Leu Cys Gly His Asp Ala Val Arg Glu Ala Leu Val Asp Gln Ala Glu
                85                  90                  95

Glu Phe Ser Gly Arg Gly Glu Gln Ala Thr Phe Asp Trp Val Phe Lys
            100                 105                 110
```

```
Gly Tyr Gly Val Val Phe Ser Asn Gly Glu Arg Ala Lys Gln Leu Arg
        115                 120                 125

Arg Phe Ser Ile Ala Thr Leu Arg Asp Phe Gly Val Gly Lys Arg Gly
    130                 135                 140

Ile Glu Glu Arg Ile Gln Glu Glu Ala Gly Phe Leu Ile Asp Ala Leu
145                 150                 155                 160

Arg Gly Thr Gly Gly Ala Asn Ile Asp Pro Thr Phe Phe Leu Ser Arg
                165                 170                 175

Thr Val Ser Asn Val Ile Ser Ser Ile Val Phe Gly Asp Arg Phe Asp
            180                 185                 190

Tyr Lys Asp Lys Glu Phe Leu Ser Leu Leu Arg Met Met Leu Gly Ile
        195                 200                 205

Phe Gln Phe Thr Ser Thr Ser Thr Gly Gln Leu Tyr Glu Met Phe Ser
    210                 215                 220

Ser Val Met Lys His Leu Pro Gly Pro Gln Gln Gln Ala Phe Gln Leu
225                 230                 235                 240

Leu Gln Gly Leu Glu Asp Phe Ile Ala Lys Lys Val Glu His Asn Gln
                245                 250                 255

Arg Thr Leu Asp Pro Asn Ser Pro Arg Asp Phe Ile Asp Ser Phe Leu
            260                 265                 270

Ile Arg Met Gln Glu Glu Glu Lys Asn Pro Asn Thr Glu Phe Tyr Leu
        275                 280                 285

Lys Asn Leu Val Met Thr Thr Leu Asn Leu Phe Ile Gly Gly Thr Glu
    290                 295                 300

Thr Val Ser Thr Thr Leu Arg Tyr Gly Phe Leu Leu Leu Met Lys His
305                 310                 315                 320

Pro Glu Val Glu Ala Lys Val His Glu Glu Ile Asp Arg Val Ile Gly
                325                 330                 335

Lys Asn Arg Gln Pro Lys Phe Glu Asp Arg Ala Lys Met Pro Tyr Met
            340                 345                 350

Glu Ala Val Ile His Glu Ile Gln Arg Phe Gly Asp Val Ile Pro Met
        355                 360                 365

Ser Leu Ala Arg Arg Val Lys Lys Asp Thr Lys Phe Arg Asp Phe Phe
    370                 375                 380

Leu Pro Lys Gly Thr Glu Val Tyr Pro Met Leu Gly Ser Val Leu Arg
385                 390                 395                 400

Asp Pro Ser Phe Phe Ser Asn Pro Gln Asp Phe Asn Pro Gln His Phe
                405                 410                 415
```

```
Leu Asn Glu Lys Gly Gln Phe Lys Lys Ser Asp Ala Phe Val Pro Phe
            420                 425                 430

Ser Ile Gly Lys Arg Asn Cys Phe Gly Glu Gly Leu Ala Arg Met Glu
        435                 440                 445

Leu Phe Leu Phe Phe Thr Thr Val Met Gln Asn Phe Arg Leu Lys Ser
    450                 455                 460

Ser Gln Ser Pro Lys Asp Ile Asp Val Ser Pro Lys His Val Gly Phe
465                 470                 475                 480

Ala Thr Ile Pro Arg Asn Tyr Thr Met Ser Phe Leu Pro Arg
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1476 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1473

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

```
ATG GAA CTC AGC GTC CTC CTC TTC CTT GCA CTC CTC ACA GGA CTC TTG      48
Met Glu Leu Ser Val Leu Leu Phe Leu Ala Leu Leu Thr Gly Leu Leu
  1               5                  10                  15

CTA CTC CTG GTT CAG CGC CAC CCT AAC ACC CAT GAC CGC CTC CCA CCA      96
Leu Leu Leu Val Gln Arg His Pro Asn Thr His Asp Arg Leu Pro Pro
            20                  25                  30

GGG CCC CGC CCT CTG CCC CTT TTG GGA AAC CTT CTG CAG ATG GAT AGA     144
Gly Pro Arg Pro Leu Pro Leu Leu Gly Asn Leu Leu Gln Met Asp Arg
        35                  40                  45

AGA GGC CTA CTC AAA TCC TTT CTG AGG TTC CGA GAG AAA TAT GGG GAC     192
Arg Gly Leu Leu Lys Ser Phe Leu Arg Phe Arg Glu Lys Tyr Gly Asp
    50                  55                  60

GTC TTC ACG GTA CAC CTG GGA CCG AGG CCC GTG GTC ATG CTG TGT GGA     240
Val Phe Thr Val His Leu Gly Pro Arg Pro Val Val Met Leu Cys Gly
65                  70                  75                  80

GTA GAG GCC ATA CGG GAG GCC CTT GTG GAC AAG GCT GAG GCC TTC TCT     288
Val Glu Ala Ile Arg Glu Ala Leu Val Asp Lys Ala Glu Ala Phe Ser
                85                  90                  95

GGC CGG GGA AAA ATC GCC ATG GTC GAC CCA TTC TTC CGG GGA TAT GGT     336
Gly Arg Gly Lys Ile Ala Met Val Asp Pro Phe Phe Arg Gly Tyr Gly
            100                 105                 110
```

```
GTG ATC TTT GCC AAT GGA AAC CGC TGG AAG GTG CTT CGG CGA TTC TCT      384
Val Ile Phe Ala Asn Gly Asn Arg Trp Lys Val Leu Arg Arg Phe Ser
        115                 120                 125

GTG ACC ACT ATG AGG GAC TTC GGG ATG GGA AAG CGG AGT GTG GAG GAG      432
Val Thr Thr Met Arg Asp Phe Gly Met Gly Lys Arg Ser Val Glu Glu
    130                 135                 140

CGG ATT CAG GAG GAG GCT CAG TGT CTG ATA GAG GAG CTT CGG AAA TCC      480
Arg Ile Gln Glu Glu Ala Gln Cys Leu Ile Glu Glu Leu Arg Lys Ser
145                 150                 155                 160

AAG GGG GCC CTC ATG GAC CCC ACC TTC CTC TTC CAG TCC ATT ACC GCC      528
Lys Gly Ala Leu Met Asp Pro Thr Phe Leu Phe Gln Ser Ile Thr Ala
                165                 170                 175

AAC ATC ATC TGC TCC ATC GTC TTT GGA AAA CGA TTC CAC TAC CAA GAT      576
Asn Ile Ile Cys Ser Ile Val Phe Gly Lys Arg Phe His Tyr Gln Asp
            180                 185                 190

CAA GAG TTC CTG AAG ATG CTG AAC TTG TTC TAC CAG ACT TTT TCA CTC      624
Gln Glu Phe Leu Lys Met Leu Asn Leu Phe Tyr Gln Thr Phe Ser Leu
        195                 200                 205

ATC AGC TCT GTA TTC GGC CAG CTG TTT GAG CTC TTC TCT GGC TTC TTG      672
Ile Ser Ser Val Phe Gly Gln Leu Phe Glu Leu Phe Ser Gly Phe Leu
    210                 215                 220

AAA TAC TTT CCT GGG GCA CAC AGG CAA GTT TAC AAA AAC CTG CAG GAA      720
Lys Tyr Phe Pro Gly Ala His Arg Gln Val Tyr Lys Asn Leu Gln Glu
225                 230                 235                 240

ATC AAT GCT TAC ATT GGC CAC AGT GTG GAG AAG CAC CGT GAA ACC CTG      768
Ile Asn Ala Tyr Ile Gly His Ser Val Glu Lys His Arg Glu Thr Leu
                245                 250                 255

GAC CCC AGC GCC CCC AAG GAC CTC ATC GAC ACC TAC CTG CTC CAC ATG      816
Asp Pro Ser Ala Pro Lys Asp Leu Ile Asp Thr Tyr Leu Leu His Met
            260                 265                 270

GAA AAA GAG AAA TCC AAC GCA CAC AGT GAA TTC AGC CAC CAG AAC CTC      864
Glu Lys Glu Lys Ser Asn Ala His Ser Glu Phe Ser His Gln Asn Leu
        275                 280                 285

AAC CTC AAC ACG CTC TCG CTC TTC TTT GCT GGC ACT GAG ACC ACC AGC      912
Asn Leu Asn Thr Leu Ser Leu Phe Phe Ala Gly Thr Glu Thr Thr Ser
    290                 295                 300

ACC ACT CTC CGC TAC GGC TTC CTG CTC ATG CTC AAA TAC CCT CAT GTT      960
Thr Thr Leu Arg Tyr Gly Phe Leu Leu Met Leu Lys Tyr Pro His Val
305                 310                 315                 320

GCA GAG AGA GTC TAC AGG GAG ATT GAA CAG GTG ATT GGC CCA CAT CGC     1008
Ala Glu Arg Val Tyr Arg Glu Ile Glu Gln Val Ile Gly Pro His Arg
                325                 330                 335

CCT CCA GAG CTT CAT GAC CGA GCC AAA ATG CCA TAC ACA GAG GCA GTC     1056
Pro Pro Glu Leu His Asp Arg Ala Lys Met Pro Tyr Thr Glu Ala Val
            340                 345                 350
```

```
ATC TAT GAG ATT CAG AGA TTT TCC GAC CTT CTC CCC ATG GGT GTG CCC      1104
Ile Tyr Glu Ile Gln Arg Phe Ser Asp Leu Leu Pro Met Gly Val Pro
        355                 360                 365

CAC ATT GTC ACC CAA CAC ACC AGC TTC CGA GGG TAC ATC ATC CCC AAG      1152
His Ile Val Thr Gln His Thr Ser Phe Arg Gly Tyr Ile Ile Pro Lys
    370                 375                 380

GAC ACA GAA GTA TTT CTC ATC CTG AGC ACT GCT CTC CAT GAC CCA CAC      1200
Asp Thr Glu Val Phe Leu Ile Leu Ser Thr Ala Leu His Asp Pro His
385                 390                 395                 400

TAC TTT GAA AAA CCA GAC GCC TTC AAT CCT GAC CAC TTT CTG GAT GCC      1248
Tyr Phe Glu Lys Pro Asp Ala Phe Asn Pro Asp His Phe Leu Asp Ala
                405                 410                 415

AAT GGG GCA CTG AAA AAG ACT GAA GCT TTT ATC CCC TTC TCC TTA GGG      1296
Asn Gly Ala Leu Lys Lys Thr Glu Ala Phe Ile Pro Phe Ser Leu Gly
            420                 425                 430

AAG CGG ATT TGT CTT GGT GAA GGC ATC GCC CGT GCG GAA TTG TTC CTC      1344
Lys Arg Ile Cys Leu Gly Glu Gly Ile Ala Arg Ala Glu Leu Phe Leu
        435                 440                 445

TTC TTC ACC ACC ATC CTC CAG AAC TTC TCC ATG GCC AGC CCC GTG GCC      1392
Phe Phe Thr Thr Ile Leu Gln Asn Phe Ser Met Ala Ser Pro Val Ala
    450                 455                 460

CCA GAA GAC ATC GAT CTG ACA CCC CAG GAG TGT GGT GTG GGC AAA ATA      1440
Pro Glu Asp Ile Asp Leu Thr Pro Gln Glu Cys Gly Val Gly Lys Ile
465                 470                 475                 480

CCC CCA ACA TAC CAG ATC CGC TTC CTG CCC CGC TGA                      1476
Pro Pro Thr Tyr Gln Ile Arg Phe Leu Pro Arg
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 491 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

```
Met Glu Leu Ser Val Leu Leu Phe Leu Ala Leu Leu Thr Gly Leu Leu
  1               5                  10                  15

Leu Leu Leu Val Gln Arg His Pro Asn Thr His Asp Arg Leu Pro Pro
            20                  25                  30

Gly Pro Arg Pro Leu Pro Leu Leu Gly Asn Leu Leu Gln Met Asp Arg
        35                  40                  45
```

```
Arg Gly Leu Leu Lys Ser Phe Leu Arg Phe Arg Glu Lys Tyr Gly Asp
 50                  55                  60

Val Phe Thr Val His Leu Gly Pro Arg Pro Val Val Met Leu Cys Gly
65                  70                  75                  80

Val Glu Ala Ile Arg Glu Ala Leu Val Asp Lys Ala Glu Ala Phe Ser
                85                  90                  95

Gly Arg Gly Lys Ile Ala Met Val Asp Pro Phe Phe Arg Gly Tyr Gly
            100                 105                 110

Val Ile Phe Ala Asn Gly Asn Arg Trp Lys Val Leu Arg Arg Phe Ser
        115                 120                 125

Val Thr Thr Met Arg Asp Phe Gly Met Gly Lys Arg Ser Val Glu Glu
    130                 135                 140

Arg Ile Gln Glu Glu Ala Gln Cys Leu Ile Glu Glu Leu Arg Lys Ser
145                 150                 155                 160

Lys Gly Ala Leu Met Asp Pro Thr Phe Leu Phe Gln Ser Ile Thr Ala
                165                 170                 175

Asn Ile Ile Cys Ser Ile Val Phe Gly Lys Arg Phe His Tyr Gln Asp
            180                 185                 190

Gln Glu Phe Leu Lys Met Leu Asn Leu Phe Tyr Gln Thr Phe Ser Leu
        195                 200                 205

Ile Ser Ser Val Phe Gly Gln Leu Phe Glu Leu Phe Ser Gly Phe Leu
    210                 215                 220

Lys Tyr Phe Pro Gly Ala His Arg Gln Val Tyr Lys Asn Leu Gln Glu
225                 230                 235                 240

Ile Asn Ala Tyr Ile Gly His Ser Val Glu Lys His Arg Glu Thr Leu
                245                 250                 255

Asp Pro Ser Ala Pro Lys Asp Leu Ile Asp Thr Tyr Leu Leu His Met
            260                 265                 270

Glu Lys Glu Lys Ser Asn Ala His Ser Glu Phe Ser His Gln Asn Leu
        275                 280                 285

Asn Leu Asn Thr Leu Ser Leu Phe Phe Ala Gly Thr Glu Thr Thr Ser
    290                 295                 300

Thr Thr Leu Arg Tyr Gly Phe Leu Leu Met Leu Lys Tyr Pro His Val
305                 310                 315                 320

Ala Glu Arg Val Tyr Arg Glu Ile Glu Gln Val Ile Gly Pro His Arg
                325                 330                 335

Pro Pro Glu Leu His Asp Arg Ala Lys Met Pro Tyr Thr Glu Ala Val
            340                 345                 350

Ile Tyr Glu Ile Gln Arg Phe Ser Asp Leu Leu Pro Met Gly Val Pro
        355                 360                 365
```

```
His Ile Val Thr Gln His Thr Ser Phe Arg Gly Tyr Ile Ile Pro Lys
    370                 375                 380

Asp Thr Glu Val Phe Leu Ile Leu Ser Thr Ala Leu His Asp Pro His
385                 390                 395                 400

Tyr Phe Glu Lys Pro Asp Ala Phe Asn Pro Asp His Phe Leu Asp Ala
                405                 410                 415

Asn Gly Ala Leu Lys Lys Thr Glu Ala Phe Ile Pro Phe Ser Leu Gly
            420                 425                 430

Lys Arg Ile Cys Leu Gly Glu Gly Ile Ala Arg Ala Glu Leu Phe Leu
        435                 440                 445

Phe Phe Thr Thr Ile Leu Gln Asn Phe Ser Met Ala Ser Pro Val Ala
    450                 455                 460

Pro Glu Asp Ile Asp Leu Thr Pro Gln Glu Cys Gly Val Gly Lys Ile
465                 470                 475                 480

Pro Pro Thr Tyr Gln Ile Arg Phe Leu Pro Arg
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

```
ATG GAA CCT TTT GTG GTC CTG GTG CTG TGT CTC TCT TTT ATG CTT CTC        48
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
  1               5                  10                  15

TTT TCA CTC TGG AGA CAG AGC TGT AGG AGA AGG AAG CTC CCT CCT GGC        96
Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30

CCC ACT CCT CTT CCT ATT ATT GGA AAT ATG CTA CAG ATA GAT GTT AAG       144
Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
        35                  40                  45

GAC ATC TGC AAA TCT TTC ACC AAT TTC TCA AAA GTC TAT GGT CCT GTG       192
Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60
```

```
TTC ACC GTG TAT TTT GGC ATG AAT CCC ATA GTG GTG TTT CAT GGA TAT        240
Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
 65                  70                  75                  80

GAG GCA GTG AAG GAA GCC CTG ATT GAT AAT GGA GAG GAG TTT TCT GGA        288
Glu Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                 85                  90                  95

AGA GGC AAT TCC CCA ATA TCT CAA AGA ATT ACT AAA GGA CTT GGA ATC        336
Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

ATT TCC AGC AAT GGA AAG AGA TGG AAG GAG ATC CGG CGT TTC TCC CTC        384
Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

ACA ACC TTG CGG AAT TTT GGG ATG GGG AAG AGG AGC ATT GAG GAC CGT        432
Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

GTT CAA GAG GAA GCT CAC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAG        480
Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

GCT TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT        528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCC GTT GTT TTC CAG AAA CGA TTT GAT TAT AAA GAT CAG        576
Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

AAT TTT CTC ACC CTG ATG AAA AGA TTC AAT GAA AAC TTC AGG ATT CTG        624
Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205

AAC TCC CCA TGG ATC CAG GTC TGC AAT AAT TTC CCT CTA CTC ATT GAT        672
Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

TGT TTC CCA GGA ACT CAC AAC AAA GTG CTT AAA AAT GTT GCT CTT ACA        720
Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240

CGA AGT TAC ATT AGG GAG AAA GTA AAA GAA CAC CAA GCA TCA CTG GAT        768
Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255

GTT AAC AAT CCT CGG GAC TTT ATC GAT TGC TTC CTG ATC AAA ATG GAG        816
Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

CAG GAA AAG GAC AAC CAA AAG TCA GAA TTC AAT ATT GAA AAC TTG GTT        864
Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

GGC ACT GTA GCT GAT CTA TTT GTT GCT GGA ACA GAG ACA ACA AGC ACC        912
Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300
```

```
ACT CTG AGA TAT GGA CTC CTG CTC CTG CTG AAG CAC CCA GAG GTC ACA        960
Thr Leu Arg Tyr Gly Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAT CAT GTA ATT GGC AGA CAC AGG AGC       1008
Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

CCC TGC ATG CAG GAT AGG AGC CAC ATG CCT TAC ACT GAT GCT GTA GTG       1056
Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

CAC GAG ATC CAG AGA TAC AGT GAC CTT GTC CCC ACC GGT GTG CCC CAT       1104
His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

GCA GTG ACC ACT GAT ACT AAG TTC AGA AAC TAC CTC ATC CCC AAG GGC       1152
Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

ACA ACC ATA ATG GCA TTA CTG ACT TCC GTG CTA CAT GAT GAC AAA GAA       1200
Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Lys Glu
385                 390                 395                 400

TTT CCT AAT CCA AAT ATC TTT GAC CCT GGC CAC TTT CTA GAT AAG AAT       1248
Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

GGC AAC TTT AAG AAA AGT GAC TAC TTC ATG CCT TTC TCA GCA GGA AAA       1296
Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGA ATT TGT GCA GGA GAA GGA CTT GCC CGC ATG GAG CTA TTT TTA TTT       1344
Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

CTA ACC ACA ATT TTA CAG AAC TTT AAC CTG AAA TCT GTT GAT GAT TTA       1392
Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

AAG AAC CTC AAT ACT ACT GCA GTT ACC AAA GGG ATT GTT TCT CTG CCA       1440
Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

CCC TCA TAC CAG ATC TGC TTC ATC CCT GTC TGA                           1473
Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

```
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
 1               5                  10                  15

Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30

Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
        35                  40                  45

Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
65                  70                  75                  80

Glu Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                85                  90                  95

Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205

Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240

Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255

Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300
```

```
Thr Leu Arg Tyr Gly Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Lys Glu
385                 390                 395                 400

Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

```
ATG GAA CCT TTT GTG GTC CTG GTG CTG TGT CTC TCT TTT ATG CTT CTC        48
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
 1               5                  10                  15

TTT TCA CTC TGG AGA CAG AGC TGT AGG AGA AGG AAG CTC CCT CCT GGC        96
Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30
```

```
CCC ACT CCT CTT CCT ATT ATT GGA AAT ATG CTA CAG ATA GAT GTT AAG        144
Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
         35                  40                  45

GAC ATC TGC AAA TCT TTC ACC AAT TTC TCA AAA GTC TAT GGT CCT GTG        192
Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
      50                  55                  60

TTC ACC GTG TAT TTT GGC ATG AAT CCC ATA GTG GTG TTT CAT GGA TAT        240
Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
 65                  70                  75                  80

GAG GCA GTG AAG GAA GCC CTG ATT GAT AAT GGA GAG GAG TTT TCT GGA        288
Glu Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                 85                  90                  95

AGA GGC AAT TCC CCA ATA TCT CAA AGA ATT ACT AAA GGA CTT GGA ATC        336
Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

ATT TCC AGC AAT GGA AAG AGA TGG AAG GAG ATC CGG CGT TTC TCC CTC        384
Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

ACA ACC TTG CGG AAT TTT GGG ATG GGG AAG AAG AGC ATT GAG GAC CGT        432
Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Lys Ser Ile Glu Asp Arg
    130                 135                 140

GTT CAA GAG GAA GCT CAC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAG        480
Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

GCT TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT        528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCC GTT GTT TTC CAG AAA CGA TTT GAT TAT AAA GAT CAG        576
Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

AAT TTT CTC ACC CTG ATG AAA AGA TTC AAT GAA AAC TTC AGG ATT CTG        624
Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205

AAC TCC CCA TGG ATC CAG GTC TGC AAT AAT TTC CCT CTA CTC ATT GAT        672
Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

TGT TTC CCA GGA ACT CAC AAC AAA GTG CTT AAA AAT GTT GCT CTT ACA        720
Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240

CGA AGT TAC ATT AGG GAG AAA GTA AAA GAA CAC CAA GCA TCA CTG GAT        768
Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255
```

```
GTT AAC AAT CCT CGG GAC TTT ATC GAT TGC TTC CTG ATC AAA ATG GAG        816
Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

CAG GAA AAG GAC AAC CAA AAG TCA GAA TTC AAT ATT GAA AAC TTG GTT        864
Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

GGC ACT GTA GCT GAT CTA TTT GTT GCT GGA ACA GAG ACA ACA AGC ACC        912
Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

ACT CTG AGA TAT GGA CTC CTG CTC CTG CTG AAG CAC CCA GAG GTC ACA        960
Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAT CAT GTA ATT GGC AGA CAC AGG AGC       1008
Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

CCC TGC ATG CAG GAT AGG AGC CAC ATG CCT TAC ACT GAT GCT GTA GTG       1056
Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

CAC GAG ATC CAG AGA TAC AGT GAC CTT GTC CCC ACC GGT GTG CCC CAT       1104
His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

GCA GTG ACC ACT GAT ACT AAG TTC AGA AAC TAC CTC ATC CCC AAG GGC       1152
Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

ACA ACC ATA ATG GCA TTA CTG ACT TCC GTG CTA CAT GAT GAC AGA GAA       1200
Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Arg Glu
385                 390                 395                 400

TTT CCT AAT CCA AAT ATC TTT GAC CCT GGC CAC TTT CTA GAT AAG AAT       1248
Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

GGC AAC TTT AAG AAA AGT GAC TAC TTC ATG CCT TTC TCA GCA GGA AAA       1296
Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGA ATT TGT GCA GGA GAA GGA CTT GCC CGC ATG GAG CTA TTT TTA TTT       1344
Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

CTA ACC ACA ATT TTA CAG AAC TTT AAC CTG AAA TCT GTT GAT GAT TTA       1392
Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

AAG AAC CTC AAT ACT ACT GCA GTT ACC AAA GGG ATT GTT TCT CTG CCA       1440
Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

CCC TCA TAC CAG ATC TGC TTC ATC CCT GTC TGA                           1473
Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

```
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
 1               5                  10                  15

Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30

Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
        35                  40                  45

Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
65                  70                  75                  80

Glu Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                85                  90                  95

Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Lys Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205

Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240
```

```
Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255

Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Arg Glu
385                 390                 395                 400

Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

```
ATG GAA CCT TTT GTG GTC CTG GTG CTG TGT CTC TCT TTT ATG CTT CTC          48
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
  1               5                  10                  15

TTT TCA CTC TGG AGA CAG AGC TGT AGG AGA AGG AAG CTC CCT CCT GGC          96
Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30

CCC ACT CCT CTT CCT ATT ATT GGA AAT ATG CTA CAG ATA GAT GTT AAG         144
Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
        35                  40                  45

GAC ATC TGC AAA TCT TTC ACC AAT TTC TCA AAA GTC TAT GGT CCT GTG         192
Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

TTC ACC GTG TAT TTT GGC ATG AAT CCC ATA GTG GTG TTT CAT GGA TAT         240
Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
65                  70                  75                  80

GTG GCA GTG AAG GAA GCC CTG ATT GAT AAT GGA GAG GAG TTT TCT GGA         288
Val Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                85                  90                  95

AGA GGC AAT TCC CCA ATA TCT CAA AGA ATT ACT AAA GGA CTT GGA ATC         336
Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

ATT TCC AGC AAT GGA AAG AGA TGG AAG GAG ATC CGG CGT TTC TCC CTC         384
Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

ACA ACC TTG CGG AAT TTT GGG ATG GGG AAG AAG AGC ATT GAG GAC CGT         432
Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Lys Ser Ile Glu Asp Arg
    130                 135                 140

GTT CAA GAG GAA GCT CAC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAG         480
Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

GCT TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT         528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCC GTT GTT TTC CAG AAA CGA TTT GAT TAT AAA GAT CAG         576
Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

AAT TTT CTC ACC CTG ATG AAA AGA TTC AAT GAA AAC TTC AGG ATT CTG         624
Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205
```

```
AAC TCC CCA TGG ATC CAG GTC TGC AAT AAT TTC CCT CTA CTC ATT GAT      672
Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

TGT TTC CCA GGA ACT CAC AAC AAA GTG CTT AAA AAT GTT GCT CTT ACA      720
Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240

CGA AGT TAC ATT AGG GAG AAA GTA AAA GAA CAC CAA GCA TCA CTG GAT      768
Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255

GTT AAC AAT CCT CGG GAC TTT ATC GAT TGC TTC CTG ATC AAA ATG GAG      816
Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

CAG GAA AAG GAC AAC CAA AAG TCA GAA TTC AAT ATT GAA AAC TTG GTT      864
Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

GGC ACT GTA GCT GAT CTA TTT GTT GCT GGA ACA GAG ACA ACA AGC ACC      912
Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

ACT CTG AGA TAT GGA CTC CTG CTC CTG CTG AAG CAC CCA GAG GTC ACA      960
Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAT CAT GTA ATT GGC AGA CAC AGG AGC     1008
Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

CCC TGC ATG CAG GAT AGG AGC CAC ATG CCT TAC ACT GAT GCT GTA GTG     1056
Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

CAC GAG ATC CAG AGA TAC AGT GAC CTT GTC CCC ACC GGT GTG CCC CAT     1104
His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

GCA GTG ACC ACT GAT ACT AAG TTC AGA AAC TAC CTC ATC CCC AAG GGC     1152
Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

ACA ACC ATA ATG GCA TTA CTG ACT TCC GTG CTA CAT GAT GAC AGA GAA     1200
Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Arg Glu
385                 390                 395                 400

TTT CCT AAT CCA AAT ATC TTT GAC CCT GGC CAC TTT CTA GAT AAG AAT     1248
Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

GGC AAC TTT AAG AAA AGT GAC TAC TTC ATG CCT TTC TCA GCA GGA AAA     1296
Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGA ATT TGT GCA GGA GAA GGA CTT GCC CGC ATG GAG CTA TTT TTA TTT     1344
Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445
```

```
CTA ACC ACA ATT TTA CAG AAC TTT AAC CTG AAA TCT GTT GAT GAT TTA      1392
Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

AAG AAC CTC AAT ACT ACT GCA GTT ACC AAA GGG ATT GTT TCT CTG CCA      1440
Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

CCC TCA TAC CAG ATC TGC TTC ATC CCT GTC TGA                          1473
Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

```
Met Glu Pro Phe Val Val Leu Val Leu Cys Leu Ser Phe Met Leu Leu
 1               5                  10                  15

Phe Ser Leu Trp Arg Gln Ser Cys Arg Arg Arg Lys Leu Pro Pro Gly
            20                  25                  30

Pro Thr Pro Leu Pro Ile Ile Gly Asn Met Leu Gln Ile Asp Val Lys
        35                  40                  45

Asp Ile Cys Lys Ser Phe Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

Phe Thr Val Tyr Phe Gly Met Asn Pro Ile Val Val Phe His Gly Tyr
65                  70                  75                  80

Val Ala Val Lys Glu Ala Leu Ile Asp Asn Gly Glu Glu Phe Ser Gly
                85                  90                  95

Arg Gly Asn Ser Pro Ile Ser Gln Arg Ile Thr Lys Gly Leu Gly Ile
            100                 105                 110

Ile Ser Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

Thr Thr Leu Arg Asn Phe Gly Met Gly Lys Lys Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala His Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175
```

```
Val Ile Cys Ser Val Val Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Asn Phe Leu Thr Leu Met Lys Arg Phe Asn Glu Asn Phe Arg Ile Leu
        195                 200                 205

Asn Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Leu Leu Ile Asp
    210                 215                 220

Cys Phe Pro Gly Thr His Asn Lys Val Leu Lys Asn Val Ala Leu Thr
225                 230                 235                 240

Arg Ser Tyr Ile Arg Glu Lys Val Lys Glu His Gln Ala Ser Leu Asp
                245                 250                 255

Val Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

Gln Glu Lys Asp Asn Gln Lys Ser Glu Phe Asn Ile Glu Asn Leu Val
        275                 280                 285

Gly Thr Val Ala Asp Leu Phe Val Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Asp His Val Ile Gly Arg His Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Ile Gln Arg Tyr Ser Asp Leu Val Pro Thr Gly Val Pro His
        355                 360                 365

Ala Val Thr Thr Asp Thr Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Met Ala Leu Leu Thr Ser Val Leu His Asp Asp Arg Glu
385                 390                 395                 400

Phe Pro Asn Pro Asn Ile Phe Asp Pro Gly His Phe Leu Asp Lys Asn
                405                 410                 415

Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

Arg Ile Cys Ala Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Val Asp Asp Leu
    450                 455                 460

Lys Asn Leu Asn Thr Thr Ala Val Thr Lys Gly Ile Val Ser Leu Pro
465                 470                 475                 480

Pro Ser Tyr Gln Ile Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

```
ATG GAT CCA GCT GTG GCT CTG GTG CTC TGT CTC TCC TGT TTG TTT CTC        48
Met Asp Pro Ala Val Ala Leu Val Leu Cys Leu Ser Cys Leu Phe Leu
 1               5                  10                  15

CTT TCA CTC TGG AGG CAG AGC TCT GGA AGA GGG AGG CTC CCG TCT GGC        96
Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Arg Leu Pro Ser Gly
            20                  25                  30

CCC ACT CCT CTC CCG ATT ATT GGA AAT ATC CTG CAG TTA GAT GTT AAG       144
Pro Thr Pro Leu Pro Ile Ile Gly Asn Ile Leu Gln Leu Asp Val Lys
        35                  40                  45

GAC ATG AGC AAA TCC TTA ACC AAT TTC TCA AAA GTC TAT GGC CCT GTG       192
Asp Met Ser Lys Ser Leu Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

TTC ACT GTG TAT TTT GGC CTG AAG CCC ATT GTG GTG TTG CAT GGA TAT       240
Phe Thr Val Tyr Phe Gly Leu Lys Pro Ile Val Val Leu His Gly Tyr
65                  70                  75                  80

GAA GCA GTG AAG GAG GCC CTG ATT GAT CAT GGA GAG GAG TTT TCT GGA       288
Glu Ala Val Lys Glu Ala Leu Ile Asp His Gly Glu Glu Phe Ser Gly
                85                  90                  95

AGA GGA AGT TTT CCA GTG GCT GAA AAA GTT AAC AAA GGA CTT GGA ATC       336
Arg Gly Ser Phe Pro Val Ala Glu Lys Val Asn Lys Gly Leu Gly Ile
            100                 105                 110

CTT TTC AGC AAT GGA AAG AGA TGG AAG GAG ATC CGG CGT TTC TGC CTC       384
Leu Phe Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Cys Leu
        115                 120                 125

ATG ACT CTG CGG AAT TTT GGG ATG GGG AAG AGG AGC ATC GAG GAC CGT       432
Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

GTT CAA GAG GAA GCC CGC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAT       480
Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Asn
145                 150                 155                 160
```

```
GCC TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT      528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCT GTT ATT TTC CAT GAT CGA TTT GAT TAT AAA GAT CAG      576
Val Ile Cys Ser Val Ile Phe His Asp Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

AGG TTT CTT AAC TTG ATG GAA AAA TTC AAT GAA AAC CTC AGG ATT CTG      624
Arg Phe Leu Asn Leu Met Glu Lys Phe Asn Glu Asn Leu Arg Ile Leu
        195                 200                 205

AGC TCT CCA TGG ATC CAG GTC TGC AAT AAT TTC CCT GCT CTC ATC GAT      672
Ser Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Ala Leu Ile Asp
    210                 215                 220

TAT CTC CCA GGA AGT CAT AAT AAA ATA GCT GAA AAT TTT GCT TAC ATT      720
Tyr Leu Pro Gly Ser His Asn Lys Ile Ala Glu Asn Phe Ala Tyr Ile
225                 230                 235                 240

AAA AGT TAT GTA TTG GAG AGA ATA AAA GAA CAT CAA GAA TCC CTG GAC      768
Lys Ser Tyr Val Leu Glu Arg Ile Lys Glu His Gln Glu Ser Leu Asp
                245                 250                 255

ATG AAC AGT GCT CGG GAC TTT ATT GAT TGT TTC CTG ATC AAA ATG GAA      816
Met Asn Ser Ala Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

CAG GAA AAG CAC AAT CAA CAG TCT GAA TTT ACT GTT GAA AGC TTG ATA      864
Gln Glu Lys His Asn Gln Gln Ser Glu Phe Thr Val Glu Ser Leu Ile
        275                 280                 285

GCC ACT GTA ACT GAT ATG TTT GGG GCT GGA ACA GAG ACA ACG AGC ACC      912
Ala Thr Val Thr Asp Met Phe Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

ACT CTG AGA TAT GGA CTC CTG CTC CTG CTG AAG TAC CCA GAG GTC ACA      960
Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys Tyr Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAA TGT GTA GTT GGC AGA AAC CGG AGC     1008
Ala Lys Val Gln Glu Glu Ile Glu Cys Val Val Gly Arg Asn Arg Ser
                325                 330                 335

CCC TGT ATG CAG GAC AGG AGT CAC ATG CCC TAC ACA GAT GCT GTG GTG     1056
Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

CAC GAG ATC CAG AGA TAC ATT GAC CTC CTC CCC ACC AAC CTG CCC CAT     1104
His Glu Ile Gln Arg Tyr Ile Asp Leu Leu Pro Thr Asn Leu Pro His
        355                 360                 365

GCA GTG ACC TGT GAT GTT AAA TTC AAA AAC TAC CTC ATC CCC AAG GGC     1152
Ala Val Thr Cys Asp Val Lys Phe Lys Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

ACG ACC ATA ATA ACA TCC CTG ACT TCT GTG CTG CAC AAT GAC AAA GAA     1200
Thr Thr Ile Ile Thr Ser Leu Thr Ser Val Leu His Asn Asp Lys Glu
385                 390                 395                 400
```

```
TTC CCC AAC CCA GAG ATG TTT GAC CCT GGC CAC TTT CTG GAT AAG AGT      1248
Phe Pro Asn Pro Glu Met Phe Asp Pro Gly His Phe Leu Asp Lys Ser
                405                 410                 415

GGC AAC TTT AAG AAA AGT GAC TAC TTC ATG CCT TTC TCA GCA GGA AAA      1296
Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGG ATG TGT ATG GGA GAG GGC CTG GCC CGC ATG GAG CTG TTT TTA TTC      1344
Arg Met Cys Met Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

CTG ACC ACC ATT TTG CAG AAC TTT AAC CTG AAA TCT CAG GTT GAC CCA      1392
Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Gln Val Asp Pro
    450                 455                 460

AAG GAT ATT GAC ATC ACC CCC ATT GCC AAT GCA TTT GGT CGT GTG CCA      1440
Lys Asp Ile Asp Ile Thr Pro Ile Ala Asn Ala Phe Gly Arg Val Pro
465                 470                 475                 480

CCC TTG TAC CAG CTC TGC TTC ATT CCT GTC TGA                         1473
Pro Leu Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

```
Met Asp Pro Ala Val Ala Leu Val Leu Cys Leu Ser Cys Leu Phe Leu
 1               5                  10                  15

Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Arg Leu Pro Ser Gly
            20                  25                  30

Pro Thr Pro Leu Pro Ile Ile Gly Asn Ile Leu Gln Leu Asp Val Lys
        35                  40                  45

Asp Met Ser Lys Ser Leu Thr Asn Phe Ser Lys Val Tyr Gly Pro Val
    50                  55                  60

Phe Thr Val Tyr Phe Gly Leu Lys Pro Ile Val Val Leu His Gly Tyr
65                  70                  75                  80

Glu Ala Val Lys Glu Ala Leu Ile Asp His Gly Glu Glu Phe Ser Gly
                85                  90                  95

Arg Gly Ser Phe Pro Val Ala Glu Lys Val Asn Lys Gly Leu Gly Ile
            100                 105                 110
```

```
Leu Phe Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Cys Leu
        115                 120                 125

Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Asn
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

Val Ile Cys Ser Val Ile Phe His Asp Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Arg Phe Leu Asn Leu Met Glu Lys Phe Asn Glu Asn Leu Arg Ile Leu
        195                 200                 205

Ser Ser Pro Trp Ile Gln Val Cys Asn Asn Phe Pro Ala Leu Ile Asp
    210                 215                 220

Tyr Leu Pro Gly Ser His Asn Lys Ile Ala Glu Asn Phe Ala Tyr Ile
225                 230                 235                 240

Lys Ser Tyr Val Leu Glu Arg Ile Lys Glu His Gln Glu Ser Leu Asp
                245                 250                 255

Met Asn Ser Ala Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

Gln Glu Lys His Asn Gln Gln Ser Glu Phe Thr Val Glu Ser Leu Ile
        275                 280                 285

Ala Thr Val Thr Asp Met Phe Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

Thr Leu Arg Tyr Gly Leu Leu Leu Leu Leu Lys Tyr Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Glu Cys Val Val Gly Arg Asn Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Ser His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Ile Gln Arg Tyr Ile Asp Leu Leu Pro Thr Asn Leu Pro His
        355                 360                 365

Ala Val Thr Cys Asp Val Lys Phe Lys Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Ile Thr Ser Leu Thr Ser Val Leu His Asn Asp Lys Glu
385                 390                 395                 400

Phe Pro Asn Pro Glu Met Phe Asp Pro Gly His Phe Leu Asp Lys Ser
                405                 410                 415

Gly Asn Phe Lys Lys Ser Asp Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430
```

```
Arg Met Cys Met Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Thr Ile Leu Gln Asn Phe Asn Leu Lys Ser Gln Val Asp Pro
    450                 455                 460

Lys Asp Ile Asp Ile Thr Pro Ile Ala Asn Ala Phe Gly Arg Val Pro
465                 470                 475                 480

Pro Leu Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1470

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

```
ATG GAT CCT TTT GTG GTC CTT GTG CTC TGT CTC TCA TGT TTG CTT CTC        48
Met Asp Pro Phe Val Val Leu Val Leu Cys Leu Ser Cys Leu Leu Leu
  1               5                  10                  15

CTT TCA CTC TGG AGA CAG AGC TCT GGG AGA GGA AAA CTC CCT CCT GGC        96
Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Lys Leu Pro Pro Gly
            20                  25                  30

CCC ACT CCT CTC CCA GTG ATT GGA AAT ATC CTA CAG ATA GAT ATT AAG       144
Pro Thr Pro Leu Pro Val Ile Gly Asn Ile Leu Gln Ile Asp Ile Lys
        35                  40                  45

GAT GTC AGC AAA TCC TTA ACC AAT CTC TCA AAA ATC TAT GGC CCT GTG       192
Asp Val Ser Lys Ser Leu Thr Asn Leu Ser Lys Ile Tyr Gly Pro Val
    50                  55                  60

TTC ACT CTG TAT TTT GGC CTC GAG CGC ATG GTG GTG CTG CAT GGA TAT       240
Phe Thr Leu Tyr Phe Gly Leu Glu Arg Met Val Val Leu His Gly Tyr
65                  70                  75                  80

GAA GTG GTG AAG GAA GCC CTG ATT GAT CTT GGA GAG GAG TTT TCT GGA       288
Glu Val Val Lys Glu Ala Leu Ile Asp Leu Gly Glu Glu Phe Ser Gly
                85                  90                  95

AGA GGC CAT TTC CCA CTG GCT GAA AGA GCT AAC AGA GGA TTT GGA ATC       336
Arg Gly His Phe Pro Leu Ala Glu Arg Ala Asn Arg Gly Phe Gly Ile
            100                 105                 110
```

```
GTT TTC AGC AAT GGA AAG AGA TGG AAG GAG ATC CGG CGT TTC TCC CTC        384
Val Phe Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

ATG ACG CTG CGG AAT TTT GGG ATG GGG AAG AGG AGC ATT GAG GAC CGT        432
Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

GTT CAA GAG GAA GCC CGC TGC CTT GTG GAG GAG TTG AGA AAA ACC AAG        480
Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

GCT TCA CCC TGT GAT CCC ACT TTC ATC CTG GGC TGT GCT CCC TGC AAT        528
Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

GTG ATC TGC TCC ATT ATT TTC CAG AAA CGT TTC GAT TAT AAA GAT CAG        576
Val Ile Cys Ser Ile Ile Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

CAA TTT CTT AAC TTG ATG GAA AAA TTG AAT GAA AAC ATC AGG ATT GTA        624
Gln Phe Leu Asn Leu Met Glu Lys Leu Asn Glu Asn Ile Arg Ile Val
        195                 200                 205

AGC ACC CCC TGG ATC CAG ATA TGC AAT AAT TTT CCC ACT ATC ATT GAT        672
Ser Thr Pro Trp Ile Gln Ile Cys Asn Asn Phe Pro Thr Ile Ile Asp
    210                 215                 220

TAT TTC CCG GGA ACC CAT AAC AAA TTA CTT AAA AAC CTT GCT TTT ATG        720
Tyr Phe Pro Gly Thr His Asn Lys Leu Leu Lys Asn Leu Ala Phe Met
225                 230                 235                 240

GAA AGT GAT ATT TTG GAG AAA GTA AAA GAA CAC CAA GAA TCG ATG GAC        768
Glu Ser Asp Ile Leu Glu Lys Val Lys Glu His Gln Glu Ser Met Asp
                245                 250                 255

ATC AAC AAC CCT CGG GAC TTT ATT GAT TGC TTC CTG ATC AAA ATG GAG        816
Ile Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

AAG GAA AAG CAA AAC CAA CAG TCT GAA TTC ACT ATT GAA AAC TTG GTA        864
Lys Glu Lys Gln Asn Gln Gln Ser Glu Phe Thr Ile Glu Asn Leu Val
        275                 280                 285

ATC ACT GCA GCT GAC TTA CTT GGA GCT GGG ACA GAG ACA ACA AGC ACA        912
Ile Thr Ala Ala Asp Leu Leu Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

ACC CTG AGA TAT GCT CTC CTT CTC CTG CTG AAG CAC CCA GAG GTC ACA        960
Thr Leu Arg Tyr Ala Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

GCT AAA GTC CAG GAA GAG ATT GAA CGT GTC GTT GGC AGA AAC CGG AGC       1008
Ala Lys Val Gln Glu Glu Ile Glu Arg Val Val Gly Arg Asn Arg Ser
                325                 330                 335

CCC TGC ATG CAG GAC AGG GGC CAC ATG CCC TAC ACA GAT GCT GTG GTG       1056
Pro Cys Met Gln Asp Arg Gly His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350
```

```
CAC GAG GTC CAG AGA TAC ATC GAC CTC ATC CCC ACC AGC CTG CCC CAT      1104
His Glu Val Gln Arg Tyr Ile Asp Leu Ile Pro Thr Ser Leu Pro His
        355                 360                 365

GCA GTG ACC TGT GAC GTT AAA TTC AGA AAC TAC CTC ATT CCC AAG GGC      1152
Ala Val Thr Cys Asp Val Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

ACA ACC ATA TTA ACT TCC CTC ACT TCT GTG CTA CAT GAC AAC AAA GAA      1200
Thr Thr Ile Leu Thr Ser Leu Thr Ser Val Leu His Asp Asn Lys Glu
385                 390                 395                 400

TTC CCC AAC CCA GAG ATG TTT GAC CCT CGT CAC TTT CTG GAT GAA GGT      1248
Phe Pro Asn Pro Glu Met Phe Asp Pro Arg His Phe Leu Asp Glu Gly
                405                 410                 415

GGA AAT TTT AAG AAA AGT AAC TAC TTC ATG CCT TTC TCA GCA GGA AAA      1296
Gly Asn Phe Lys Lys Ser Asn Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

CGG ATT TGT GTG GGA GAG GGC CTG GCC CGC ATG GAG CTG TTT TTA TTC      1344
Arg Ile Cys Val Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

CTG ACC TTC ATT TTA CAG AAC TTT AAC CTG AAA TCT CTG ATT GAC CCA      1392
Leu Thr Phe Ile Leu Gln Asn Phe Asn Leu Lys Ser Leu Ile Asp Pro
    450                 455                 460

AAG GAC CTT GAC ACA ACT CCT GTT GTC AAT GGA TTT GCT TCT GTC CCG      1440
Lys Asp Leu Asp Thr Thr Pro Val Val Asn Gly Phe Ala Ser Val Pro
465                 470                 475                 480

CCC TTC TAT CAG CTG TGC TTC ATT CCT GTC TGA                         1473
Pro Phe Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 490 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

```
Met Asp Pro Phe Val Val Leu Val Leu Cys Leu Ser Cys Leu Leu Leu
  1               5                  10                  15

Leu Ser Leu Trp Arg Gln Ser Ser Gly Arg Gly Lys Leu Pro Pro Gly
            20                  25                  30

Pro Thr Pro Leu Pro Val Ile Gly Asn Ile Leu Gln Ile Asp Ile Lys
        35                  40                  45
```

```
Asp Val Ser Lys Ser Leu Thr Asn Leu Ser Lys Ile Tyr Gly Pro Val
 50                  55                  60

Phe Thr Leu Tyr Phe Gly Leu Glu Arg Met Val Val Leu His Gly Tyr
65                  70                  75                  80

Glu Val Val Lys Glu Ala Leu Ile Asp Leu Gly Glu Glu Phe Ser Gly
                85                  90                  95

Arg Gly His Phe Pro Leu Ala Glu Arg Ala Asn Arg Gly Phe Gly Ile
            100                 105                 110

Val Phe Ser Asn Gly Lys Arg Trp Lys Glu Ile Arg Arg Phe Ser Leu
        115                 120                 125

Met Thr Leu Arg Asn Phe Gly Met Gly Lys Arg Ser Ile Glu Asp Arg
    130                 135                 140

Val Gln Glu Glu Ala Arg Cys Leu Val Glu Glu Leu Arg Lys Thr Lys
145                 150                 155                 160

Ala Ser Pro Cys Asp Pro Thr Phe Ile Leu Gly Cys Ala Pro Cys Asn
                165                 170                 175

Val Ile Cys Ser Ile Ile Phe Gln Lys Arg Phe Asp Tyr Lys Asp Gln
            180                 185                 190

Gln Phe Leu Asn Leu Met Glu Lys Leu Asn Glu Asn Ile Arg Ile Val
        195                 200                 205

Ser Thr Pro Trp Ile Gln Ile Cys Asn Asn Phe Pro Thr Ile Ile Asp
    210                 215                 220

Tyr Phe Pro Gly Thr His Asn Lys Leu Leu Lys Asn Leu Ala Phe Met
225                 230                 235                 240

Glu Ser Asp Ile Leu Glu Lys Val Lys Glu His Gln Glu Ser Met Asp
                245                 250                 255

Ile Asn Asn Pro Arg Asp Phe Ile Asp Cys Phe Leu Ile Lys Met Glu
            260                 265                 270

Lys Glu Lys Gln Asn Gln Gln Ser Glu Phe Thr Ile Glu Asn Leu Val
        275                 280                 285

Ile Thr Ala Ala Asp Leu Leu Gly Ala Gly Thr Glu Thr Thr Ser Thr
    290                 295                 300

Thr Leu Arg Tyr Ala Leu Leu Leu Leu Leu Lys His Pro Glu Val Thr
305                 310                 315                 320

Ala Lys Val Gln Glu Glu Ile Glu Arg Val Val Gly Arg Asn Arg Ser
                325                 330                 335

Pro Cys Met Gln Asp Arg Gly His Met Pro Tyr Thr Asp Ala Val Val
            340                 345                 350

His Glu Val Gln Arg Tyr Ile Asp Leu Ile Pro Thr Ser Leu Pro His
        355                 360                 365
```

```
Ala Val Thr Cys Asp Val Lys Phe Arg Asn Tyr Leu Ile Pro Lys Gly
    370                 375                 380

Thr Thr Ile Leu Thr Ser Leu Thr Ser Val Leu His Asp Asn Lys Glu
385                 390                 395                 400

Phe Pro Asn Pro Glu Met Phe Asp Pro Arg His Phe Leu Asp Glu Gly
                405                 410                 415

Gly Asn Phe Lys Lys Ser Asn Tyr Phe Met Pro Phe Ser Ala Gly Lys
            420                 425                 430

Arg Ile Cys Val Gly Glu Gly Leu Ala Arg Met Glu Leu Phe Leu Phe
        435                 440                 445

Leu Thr Phe Ile Leu Gln Asn Phe Asn Leu Lys Ser Leu Ile Asp Pro
    450                 455                 460

Lys Asp Leu Asp Thr Thr Pro Val Val Asn Gly Phe Ala Ser Val Pro
465                 470                 475                 480

Pro Phe Tyr Gln Leu Cys Phe Ile Pro Val
                485                 490
```

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1494 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

```
ATG GGG CTA GAA GCA CTG GTG CCC CTG GCC GTG ATA GTG GCC ATC TTC        48
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
  1               5                  10                  15

CTG CTC CTG GTG GAC CTG ATG CAC CGG CGC CAA CGC TGG GCT GCA CGC        96
Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
             20                  25                  30

TAC CCA CCA GGC CCC CTG CCA CTG CCC GGG CTG GGC AAC CTG CTG CAT       144
Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
         35                  40                  45

GTG GAC TTC CAG AAC ACA CCA TAC TGC TTC GAC CAG TTG CGG CGC CGC       192
Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
     50                  55                  60
```

```
TTC GGG GAC GTG TTC AGC CTG CAG CTG GCC TGG ACG CCG GTG GTC GTG        240
Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
 65                  70                  75                  80

CTC AAT GGG CTG GCG GCC GTG CGC GAG GCG CTG GTG ACC CAC GGC GAG        288
Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

GAC ACC GCC GAC CGC CCG CCT GTG CCC ATC ACC CAG ATC CTG GGT TTC        336
Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

GGG CCG CGT TCC CAA GGG GTG TTC CTG GCG CGC TAT GGG CCC GCG TGG        384
Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

CGC GAG CAG AGG CGC TTC TCC GTC TCC ACC TTG CGC AAC TTG GGC CTG        432
Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

GGC AAG AAG TCG CTG GAG CAG TGG GTG ACC GAG GAG GCC GCC TGC CTT        480
Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

TGT GCC GCC TTC GCC AAC CAC TCC GGA CGC CCC TTT CGC CCC AAC GGT        528
Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

CTC TTG GAC AAA GCC GTG AGC AAC GTG ATC GCC TCC CTC ACC TGC GGG        576
Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

CGC CGC TTC GAA TAC GAC GAC CCT CGC TTC CTC AGG CTG CTG GAC CTA        624
Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

GCT CAG GAG GGA CTG AAG GAG GAG TCG GGC TTT CTG CGC GAG GTG CTG        672
Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

AAT GCT GTC CCC GTC CTC CTG CAT ATC CCA GCG CTG GCT GGC AAG GTC        720
Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

CTA CGC TTC CAA AAG GCT TTC CTG ACC CAG CTG GAT GAG CTG CTA ACT        768
Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

GAG CAC AGG ATG ACC TGG GAC CCA GCC CAG CCC CCC CGA GAC CTG ACT        816
Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

GAG GCC TTC CTG GCA GAG ATG GAG AAG GCC AAG GGG AAC CCT GAG AGC        864
Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

AGC TTC AAT GAT GAG AAC CTG TGC ATA GTG GTG GCT GAC CTG TTC TCT        912
Ser Phe Asn Asp Glu Asn Leu Cys Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300
```

```
GCC GGG ATG GTG ACC ACC TCG ACC ACG CTG GCC TGG GGC CTC CTG CTC        960
Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

ATG ATC CTA CAT CCG GAT GTG CAG CGC CGT GTC CAA CAG GAG ATC GAC       1008
Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

GAC GTG ATA GGG CAG GTG CGG CGA CCA GAG ATG GGT GAC CAG GCT CAC       1056
Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

ATG CCC TAC ACC ACT GCC GTG ATT CAT GAG GTG CAG CGC TTT GGG GAC       1104
Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

ATC GTC CCC CTG GGT GTG ACC CAT ATG ACA TCC CGT GAC ATC GAA GTA       1152
Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

CAG GGC TTC CGC ATC CCT AAG GGA ACG ACA CTC ATC ACC AAC CTG TCA       1200
Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

TCG GTG CTG AAG GAT GAG GCC GTC TGG GAG AAG CCC TTC CGC TTC CAC       1248
Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

CCC GAA CAC TTC CTG GAT GCC CAG GGC CAC TTT GTG AAG CCG GAG GCC       1296
Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

TTC CTG CCT TTC TCA GCA GGC CGC CGT GCA TGC CTC GGG GAG CCC CTG       1344
Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

GCC CGC ATG GAG CTC TTC CTC TTC TTC ACC TCC CTG CTG CAG CAC TTC       1392
Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

AGC TTC TCG GTG CCC ACT GGA CAG CCC CGG CCC AGC CAC CAT GGT GTC       1440
Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

TTT GCT TTC CTG GTG ACC CCA TCC CCC TAT GAG CTT TGT GCT GTG CCC       1488
Phe Ala Phe Leu Val Thr Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

CGC TAG                                                              1494
Arg
```

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 497 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

```
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
 1               5                  10                  15

Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80

Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285
```

```
Ser Phe Asn Asp Glu Asn Leu Cys Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

Phe Ala Phe Leu Val Thr Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

Arg
```

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1494 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

```
ATG GGG CTA GAA GCA CTG GTG CCC CTG GCC GTG ATA GTG GCC ATC TTC          48
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
 1               5                  10                  15

CTG CTC CTG GTG GAC CTG ATG CAC CGG CGC CAA CGC TGG GCT GCA CGC          96
Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

TAC CCA CCA GGC CCC CTG CCA CTG CCC GGG CTG GGC AAC CTG CTG CAT         144
Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

GTG GAC TTC CAG AAC ACA CCA TAC TGC TTC GAC CAG TTG CGG CGC CGC         192
Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

TTC GGG GAC GTG TTC AGC CTG CAG CTG GCC TGG ACG CCG GTG GTC GTG         240
Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80

CTC AAT GGG CTG GCG GCC GTG CGC GAG GCG CTG GTG ACC CAC GGC GAG         288
Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

GAC ACC GCC GAC CGC CCG CCT GTG CCC ATC ACC CAG ATC CTG GGT TTC         336
Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

GGG CCG CGT TCC CAA GGG GTG TTC CTG GCG CGC TAT GGG CCC GCG TGG         384
Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

CGC GAG CAG AGG CGC TTC TCC GTC TCC ACC TTG CGC AAC TTG GGC CTG         432
Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

GGC AAG AAG TCG CTG GAG CAG TGG GTG ACC GAG GAG GCC GCC TGC CTT         480
Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

TGT GCC GCC TTC GCC AAC CAC TCC GGA CGC CCC TTT CGC CCC AAC GGT         528
Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

CTC TTG GAC AAA GCC GTG AGC AAC GTG ATC GCC TCC CTC ACC TGC GGG         576
Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

CGC CGC TTC GAA TAC GAC GAC CCT CGC TTC CTC AGG CTG CTG GAC CTA         624
Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

GCT CAG GAG GGA CTG AAG GAG GAG TCG GGC TTT CTG CGC GAG GTG CTG         672
Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220
```

```
AAT GCT GTC CCC GTC CTC CTG CAT ATC CCA GCG CTG GCT GGC AAG GTC        720
Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

CTA CGC TTC CAA AAG GCT TTC CTG ACC CAG CTG GAT GAG CTG CTA ACT        768
Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

GAG CAC AGG ATG ACC TGG GAC CCA GCC CAG CCC CCC CGA GAC CTG ACT        816
Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

GAG GCC TTC CTG GCA GAG ATG GAG AAG GCC AAG GGG AAC CCT GAG AGC        864
Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

AGC TTC AAT GAT GAG AAC CTG CGC ATA GTG GTG GCT GAC CTG TTC TCT        912
Ser Phe Asn Asp Glu Asn Leu Arg Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

GCC GGG ATG GTG ACC ACC TCG ACC ACG CTG GCC TGG GGC CTC CTG CTC        960
Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

ATG ATC CTA CAT CCG GAT GTG CAG CGC CGT GTC CAA CAG GAG ATC GAC       1008
Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

GAC GTG ATA GGG CAG GTG CGG CGA CCA GAG ATG GGT GAC CAG GCT CAC       1056
Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

ATG CCC TAC ACC ACT GCC GTG ATT CAT GAG GTG CAG CGC TTT GGG GAC       1104
Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

ATC GTC CCC CTG GGT GTG ACC CAT ATG ACA TCC CGT GAC ATC GAA GTA       1152
Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

CAG GGC TTC CGC ATC CCT AAG GGA ACG ACA CTC ATC ACC AAC CTG TCA       1200
Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

TCG GTG CTG AAG GAT GAG GCC GTC TGG GAG AAG CCC TTC CGC TTC CAC       1248
Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

CCC GAA CAC TTC CTG GAT GCC CAG GGC CAC TTT GTG AAG CCG GAG GCC       1296
Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

TTC CTG CCT TTC TCA GCA GGC CGC CGT GCA TGC CTC GGG GAG CCC CTG       1344
Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

GCC CGC ATG GAG CTC TTC CTC TTC TTC ACC TCC CTG CTG CAG CAC TTC       1392
Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460
```

```
AGC TTC TCG GTG CCC ACT GGA CAG CCC CGG CCC AGC CAC CAT GGT GTC      1440
Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

TTT GCT TTC CTG GTG ACC CCA TCC CCC TAT GAG CTT TGT GCT GTG CCC      1488
Phe Ala Phe Leu Val Thr Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

CGC TAG                                                             1494
Arg
```

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 497 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

```
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
 1               5                  10                  15

Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80

Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175
```

```
Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

Ser Phe Asn Asp Glu Asn Leu Arg Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480
```

```
Phe Ala Phe Leu Val Thr Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

Arg
```

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1494 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```
ATG GGG CTA GAA GCA CTG GTG CCC CTG GCC GTG ATA GTG GCC ATC TTC   48
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
 1               5                  10                  15

CTG CTC CTG GTG GAC CTG ATG CAC CGG CGC CAA CGC TGG GCT GCA CGC   96
Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

TAC CCA CCA GGC CCC CTG CCA CTG CCC GGG CTG GGC AAC CTG CTG CAT  144
Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

GTG GAC TTC CAG AAC ACA CCA TAC TGC TTC GAC CAG TTG CGG CGC CGC  192
Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

TTC GGG GAC GTG TTC AGC CTG CAG CTG GCC TGG ACG CCG GTG GTC GTG  240
Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80

CTC AAT GGG CTG GCG GCC GTG CGC GAG GCG CTG GTG ACC CAC GGC GAG  288
Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

GAC ACC GCC GAC CGC CCG CCT GTG CCC ATC ACC CAG ATC CTG GGT TTC  336
Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

GGG CCG CGT TCC CAA GGG GTG TTC CTG GCG CGC TAT GGG CCC GCG TGG  384
Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

CGC GAG CAG AGG CGC TTC TCC GTC TCC ACC TTG CGC AAC TTG GGC CTG  432
Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140
```

```
GGC AAG AAG TCG CTG GAG CAG TGG GTG ACC GAG GAG GCC GCC TGC CTT        480
Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

TGT GCC GCC TTC GCC AAC CAC TCC GGA CGC CCC TTT CGC CCC AAC GGT        528
Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

CTC TTG GAC AAA GCC GTG AGC AAC GTG ATC GCC TCC CTC ACC TGC GGG        576
Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

CGC CGC TTC GAA TAC GAC GAC CCT CGC TTC CTC AGG CTG CTG GAC CTA        624
Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

GCT CAG GAG GGA CTG AAG GAG GAG TCG GGC TTT CTG CGC GAG GTG CTG        672
Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

AAT GCT GTC CCC GTC CTC CTG CAT ATC CCA GCG CTG GCT GGC AAG GTC        720
Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

CTA CGC TTC CAA AAG GCT TTC CTG ACC CAG CTG GAT GAG CTG CTA ACT        768
Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

GAG CAC AGG ATG ACC TGG GAC CCA GCC CAG CCC CCC CGA GAC CTG ACT        816
Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

GAG GCC TTC CTG GCA GAG ATG GAG AAG GCC AAG GGG AAC CCT GAG AGC        864
Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

AGC TTC AAT GAT GAG AAC CTG CGC ATA GTG GTG GCT GAC CTG TTC TCT        912
Ser Phe Asn Asp Glu Asn Leu Arg Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

GCC GGG ATG GTG ACC ACC TCG ACC ACG CTG GCC TGG GGC CTC CTG CTC        960
Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

ATG ATC CTA CAT CCG GAT GTG CAG CGC CGT GTC CAA CAG GAG ATC GAC       1008
Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

GAC GTG ATA GGG CAG GTG CGG CGA CCA GAG ATG GGT GAC CAG GCT CAC       1056
Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

ATG CCC TAC ACC ACT GCC GTG ATT CAT GAG GTG CAG CGC TTT GGG GAC       1104
Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

ATC GTC CCC CTG GGT GTG ACC CAT ATG ACA TCC CGT GAC ATC GAA GTA       1152
Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380
```

```
CAG GGC TTC CGC ATC CCT AAG GGA ACG ACA CTC ATC ACC AAC CTG TCA      1200
Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

TCG GTG CTG AAG GAT GAG GCC GTC TGG GAG AAG CCC TTC CGC TTC CAC      1248
Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

CCC GAA CAC TTC CTG GAT GCC CAG GGC CAC TTT GTG AAG CCG GAG GCC      1296
Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

TTC CTG CCT TTC TCA GCA GGC CGC CGT GCA TGC CTC GGG GAG CCC CTG      1344
Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

GCC CGC ATG GAG CTC TTC CTC TTC TTC ACC TCC CTG CTG CAG CAC TTC      1392
Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

AGC TTC TCG GTG CCC ACT GGA CAG CCC CGG CCC AGC CAC CAT GGT GTC      1440
Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

TTT GCT TTC CTG GTG AGC CCA TCC CCC TAT GAG CTT TGT GCT GTG CCC      1488
Phe Ala Phe Leu Val Ser Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

CGC TAG                                                             1494
Arg
```

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 497 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

```
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
  1               5                  10                  15

Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80
```

```
Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

Ser Phe Asn Asp Glu Asn Leu Arg Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380
```

```
Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

Phe Ala Phe Leu Val Ser Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

Arg
```

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1494 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1491

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

```
ATG GGG CTA GAA GCA CTG GTG CCC CTG GCC GTG ATA GTG GCC ATC TTC   48
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
  1               5                  10                  15

CTG CTC CTG GTG GAC CTG ATG CAC CGG CGC CAA CGC TGG GCT GCA CGC   96
Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

TAC CCA CCA GGC CCC CTG CCA CTG CCC GGG CTG GGC AAC CTG CTG CAT  144
Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

GTG GAC TTC CAG AAC ACA CCA TAC TGC TTC GAC CAG TTG CGG CGC CGC  192
Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

TTC GGG GAC GTG TTC AGC CTG CAG CTG GCC TGG ACG CCG GTG GTC GTG  240
Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80
```

```
CTC AAT GGG CTG GCG GCC GTG CGC GAG GCG CTG GTG ACC CAC GGC GAG        288
Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

GAC ACC GCC GAC CGC CCG CCT GTG CCC ATC ACC CAG ATC CTG GGT TTC        336
Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

GGG CCG CGT TCC CAA GGG GTG TTC CTG GCG CGC TAT GGG CCC GCG TGG        384
Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

CGC GAG CAG AGG CGC TTC TCC GTC TCC ACC TTG CGC AAC TTG GGC CTG        432
Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

GGC AAG AAG TCG CTG GAG CAG TGG GTG ACC GAG GAG GCC GCC TGC CTT        480
Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

TGT GCC GCC TTC GCC AAC CAC TCC GGA CGC CCC TTT CGC CCC AAC GGT        528
Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

CTC TTG GAC AAA GCC GTG AGC AAC GTG ATC GCC TCC CTC ACC TGC GGG        576
Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

CGC CGC TTC GAA TAC GAC GAC CCT CGC TTC CTC AGG CTG CTG GAC CTA        624
Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

GCT CAG GAG GGA CTG AAG GAG GAG TCG GGC TTT CTG CGC GAG GTG CTG        672
Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

AAT GCT GTC CCC GTC CTC CTG CAT ATC CCA GCG CTG GCT GGC AAG GTC        720
Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

CTA CGC TTC CAA AAG GCT TTC CTG ACC CAG CTG GAT GAG CTG CTA ACT        768
Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

GAG CAC AGG ATG ACC TGG GAC CCA GCC CAG CCC CCC CGA GAC CTG ACT        816
Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

GAG GCC TTC CTG GCA GAG ATG GAG AAG GCC AAG GGG AAC CCT GAG AGC        864
Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285

AGC TTC AAT GAT GAG AAC CTG TGC ATA GTG GTG GCT GAC CTG TTC TCT        912
Ser Phe Asn Asp Glu Asn Leu Cys Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300
```

```
GCC GGG ATG GTG ACC ACC TCG ACC ACG CTG GCC TGG GGC CTC CTG CTC        960
Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

ATG ATC CTA CAT CCG GAT GTG CAG CGC CGT GTC CAA CAG GAG ATC GAC       1008
Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

GAC GTG ATA GGG CAG GTG CGG CGA CCA GAG ATG GGT GAC CAG GCT CAC       1056
Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

ATG CCC TAC ACC ACT GCC GTG ATT CAT GAG GTG CAG CGC TTT GGG GAC       1104
Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

ATC GTC CCC CTG GGT GTG ACC CAT ATG ACA TCC CGT GAC ATC GAA GTA       1152
Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

CAG GGC TTC CGC ATC CCT AAG GGA ACG ACA CTC ATC ACC AAC CTG TCA       1200
Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

TCG GTG CTG AAG GAT GAG GCC GTC TGG GAG AAG CCC TTC CGC TTC CAC       1248
Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

CCC GAA CAC TTC CTG GAT GCC CAG GGC CAC TTT GTG AAG CCG GAG GCC       1296
Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

TTC CTG CCT TTC TCA GCA GGC CGC CGT GCA TGC CTC GGG GAG CCC CTG       1344
Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

GCC CGC ATG GAG CTC TTC CTC TTC TTC ACC TCC CTG CTG CAG CAC TTC       1392
Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

AGC TTC TCG GTG CCC ACT GGA CAG CCC CGG CCC AGC CAC CAT GGT GTC       1440
Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

TTT GCT TTC CTG GTG AGC CCA TCC CCC TAT GAG CTT TGT GCT GTG CCC       1488
Phe Ala Phe Leu Val Ser Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

CGC TAG                                                              1494
Arg
```

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 497 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

```
Met Gly Leu Glu Ala Leu Val Pro Leu Ala Val Ile Val Ala Ile Phe
 1               5                  10                  15

Leu Leu Leu Val Asp Leu Met His Arg Arg Gln Arg Trp Ala Ala Arg
            20                  25                  30

Tyr Pro Pro Gly Pro Leu Pro Leu Pro Gly Leu Gly Asn Leu Leu His
        35                  40                  45

Val Asp Phe Gln Asn Thr Pro Tyr Cys Phe Asp Gln Leu Arg Arg Arg
    50                  55                  60

Phe Gly Asp Val Phe Ser Leu Gln Leu Ala Trp Thr Pro Val Val Val
65                  70                  75                  80

Leu Asn Gly Leu Ala Ala Val Arg Glu Ala Leu Val Thr His Gly Glu
                85                  90                  95

Asp Thr Ala Asp Arg Pro Pro Val Pro Ile Thr Gln Ile Leu Gly Phe
            100                 105                 110

Gly Pro Arg Ser Gln Gly Val Phe Leu Ala Arg Tyr Gly Pro Ala Trp
        115                 120                 125

Arg Glu Gln Arg Arg Phe Ser Val Ser Thr Leu Arg Asn Leu Gly Leu
    130                 135                 140

Gly Lys Lys Ser Leu Glu Gln Trp Val Thr Glu Glu Ala Ala Cys Leu
145                 150                 155                 160

Cys Ala Ala Phe Ala Asn His Ser Gly Arg Pro Phe Arg Pro Asn Gly
                165                 170                 175

Leu Leu Asp Lys Ala Val Ser Asn Val Ile Ala Ser Leu Thr Cys Gly
            180                 185                 190

Arg Arg Phe Glu Tyr Asp Asp Pro Arg Phe Leu Arg Leu Leu Asp Leu
        195                 200                 205

Ala Gln Glu Gly Leu Lys Glu Glu Ser Gly Phe Leu Arg Glu Val Leu
    210                 215                 220

Asn Ala Val Pro Val Leu Leu His Ile Pro Ala Leu Ala Gly Lys Val
225                 230                 235                 240

Leu Arg Phe Gln Lys Ala Phe Leu Thr Gln Leu Asp Glu Leu Leu Thr
                245                 250                 255

Glu His Arg Met Thr Trp Asp Pro Ala Gln Pro Pro Arg Asp Leu Thr
            260                 265                 270

Glu Ala Phe Leu Ala Glu Met Glu Lys Ala Lys Gly Asn Pro Glu Ser
        275                 280                 285
```

```
Ser Phe Asn Asp Glu Asn Leu Cys Ile Val Val Ala Asp Leu Phe Ser
    290                 295                 300

Ala Gly Met Val Thr Thr Ser Thr Thr Leu Ala Trp Gly Leu Leu Leu
305                 310                 315                 320

Met Ile Leu His Pro Asp Val Gln Arg Arg Val Gln Gln Glu Ile Asp
                325                 330                 335

Asp Val Ile Gly Gln Val Arg Arg Pro Glu Met Gly Asp Gln Ala His
            340                 345                 350

Met Pro Tyr Thr Thr Ala Val Ile His Glu Val Gln Arg Phe Gly Asp
        355                 360                 365

Ile Val Pro Leu Gly Val Thr His Met Thr Ser Arg Asp Ile Glu Val
    370                 375                 380

Gln Gly Phe Arg Ile Pro Lys Gly Thr Thr Leu Ile Thr Asn Leu Ser
385                 390                 395                 400

Ser Val Leu Lys Asp Glu Ala Val Trp Glu Lys Pro Phe Arg Phe His
                405                 410                 415

Pro Glu His Phe Leu Asp Ala Gln Gly His Phe Val Lys Pro Glu Ala
            420                 425                 430

Phe Leu Pro Phe Ser Ala Gly Arg Arg Ala Cys Leu Gly Glu Pro Leu
        435                 440                 445

Ala Arg Met Glu Leu Phe Leu Phe Phe Thr Ser Leu Leu Gln His Phe
    450                 455                 460

Ser Phe Ser Val Pro Thr Gly Gln Pro Arg Pro Ser His His Gly Val
465                 470                 475                 480

Phe Ala Phe Leu Val Ser Pro Ser Pro Tyr Glu Leu Cys Ala Val Pro
                485                 490                 495

Arg
```

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

GGAACGCATG GTGGTGCTGC ATGGATATGA AGTG 34

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

CTCAAAGATC TATGGCCCTG TGTTCACTCT GTATTTTGGC CTCGAGCGCA TGGTGG 56

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

CCACCATGCG CTCGAGGCCA AAATACAG 28

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

GGGTTCCCGG GAAATAATCA ATGATAGTGG G 31

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

GGATTGTAAG CACCCCCTGG ATCCAGATAT GC 32

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

CCCAGCTCCA AGTAAGTCAG CTGCAGTGAT TACC 34

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

GGTGGTACCC TTGGGAATGA GGTAGTTTCT GAATTTAACG TC 42

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

AGTCTAGAAT GGATCCTTTT GTGGTCCTTG TGC 33

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

CCCAGAGCTC TGTCTCCAGA GTGAAAGGAG 30

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

ACAGAGCTCT GGGAGAGGAA AACTCCCTCC 30

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

CCATAGATTT TTGAGAGATT GGTTAAGGAT TTGCTGACAT CCTTAATATC TATC 54

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

GACCCTCGTC ACTTTCTGGA TGAAGGTGGA 30

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

GAAGTAGTTA CTTTTCTTAA AATTTCCACC TTCATC 36

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

AAAGAATTCC CCAACCCAGA GATGTTTGAC CCTCGTC 37

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

GGCCAGGCCC TCTCCCACAC AAATCCGTTT TCCTGCTGAG AAAGGCATGA AGTAGTTAC 59

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

GAGAGGGCCT GGCCCGCATG GAGCTGTTTT TATTCCTGAC CTTC 44

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

CAGGAGTTGT GTCAAGGTCC TTTGGGTCAA TCAG 34

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 64 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

TTGTCAATGG ATTTGCTTCT GTCCCGCCCT TCTATCAGCT GTGCTTCATT CCTGTCTGAG 60

GATC 64

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

CAGAAGCAAA TCCATTGACA ACAGGAGTTG TGTCAAGGTC CTTTGGGTCA ATCAG 55

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

CTCAGACAGG AATGAAGCAC AGCTGATAGA AGGGCGGGAC AGAAGCAAAT CCATTGACAA 60

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

GCAGCCAGAC CATCTGTGCT TCTTCAGACA GG 32

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

CACCATATTA ACTTCCCTCA CTTCTGTGCT ACATGACAAC AAAG 44

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 52 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

AATTCTTTGT TGTCATGTAG CACAGAAGTG AGGGAAGTTA ATATGGTGGT AC 52

Claims

1. A method for evaluation of the safety of a chemical compound, which comprises the steps of:
(a) reacting a chemical compound with recombinant yeast cells producing human cytochrome P450 molecular species P450 1A2, P450 2C9, P450 2E1 and P450 3A4 together with a yeast NADPH-P450 reductase, which may be in the form of a fused enzyme with each of said human cytochrome P450 molecular species, or with the cell free extracts of the yeast cells; and
(b) analyzing the resulting metabolite to determine the safety of the compound.

2. The method according to claim 1, wherein the recombinant yeast cells are yeast cells transformed with plasmids having a gene coding for human cytochrome P450 1A2, P450 2C9, P450 2E1 or P450 3A4 together with a gene coding for yeast NADPH-P450 reductase.

3. The method according to claim 1 or 2, wherein the recombinant yeast cells are yeast cells transformed with plasmids each of which has a fused gene comprising a gene coding for the human cytochrome P450 molecule on the 5'-terminal and a gene coding for the yeast NADPH-P450 reductase on 3'-terminal.

4. The method according to any one of claims 1 to 3, wherein the analyzing of the metabolite is carried out by the Ames Test.

5. The method according to claim 4, wherein the test is carried out using His^- Salmonella or Trp^- Escherichia coli.

6. The method according to any one of claims 1 to 5, wherein the recombinant yeast cells further produce at least one additional human cytochrome P450 molecular species selected from a group of human cytochrome P450 2A6, P450 2C19 and P450 2D6.

7. The method according to any one of claims 1 to 6, wherein the recombinant yeast cells further produce at least one additional human cytochrome P450 molecular species selected from a group of human cytochrome P450 1A1, P450 2B6, P450 2C8 and P450 2C18.

8. An artificial fused enzyme, which comprises human cytochrome p450 3A4 and yeast NADPH-P450 reductase.

9. A yeast expression plasmid having a fused gene comprising a gene coding for human P450 3A4 and a gene coding for the yeast NADPH-P450 reductase.

10. A method of determining in vitro the human metabolite of a chemical compound, which comprises the steps of:
(a) reacting a chemical compound with recombinant yeast cells producing human cytochrome P450 molecular species P450 1A2, P450 2C9, P450 2E1 and P450 3A4 together with a yeast NADPH-P450 reductase, which may be in the form of a fused enzyme with each of said human cytochrome P450 molecular species, or with the cell free extracts of the yeast cells; and
(b) identifying the resulting metabolite.

		Primer for amplifying
1A2	5'-CACAGAGCTCCTCCTGGCCTCTGCCATCTTC-3'	P4501A2 1.5Kb fragment
	5'-TTACAGGCCCTGCACTTGGCTAAAGCTGC-3'	
		Primer for amplifying
2C9	5'-AGTCTAGAATGGATTCTATTGTGTCCCTTGTGCTC-3'	P4502C9 0.9Kb fragment
	5'-CTCCAAACAAGTCAACTGCAGTGTTTTCCAAGC-3'	
		Primer for amplifying
	5'-GCTTGGAAAACACTGCAGTTGACTTGTTTGGAG-3'	P4502C9 0.8Kb fragment
	5'-ACTGAGCAGCAGCCAGGCCATCTGCTCTTC-3'	
		Primer for amplifying
2E1	5'-CCCCAGAATTCAATGTCTGCCCTCGGAGTG-3'	P4502E1 0.5Kb fragment
	5'-CCTCTGGATCCGGCTCTCATTGCCCTGTTTC-3'	
		Primer for amplifying
	5'-GAAACAGGGCAATGAGAGCCGGATCCAGAGG-3'	P4502E1 1.0Kb fragment
	5'-GAAAACTTGTTTGCATGCGGGGGGGTTCAGG-3'	

Fig. 1

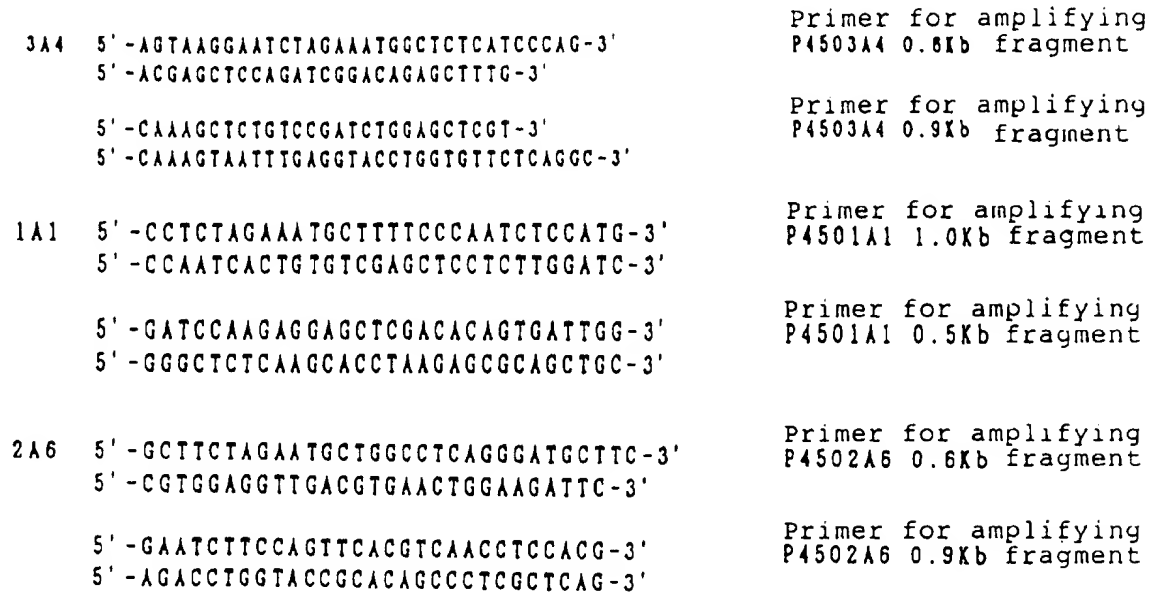

3A4
5'-AGTAAGGAATCTAGAAATGGCTCTCATCCCAG-3'
5'-ACGAGCTCCAGATCGGACAGAGCTTTG-3'
Primer for amplifying P4503A4 0.8Kb fragment
5'-CAAAGCTCTGTCCGATCTGGAGCTCGT-3'
5'-CAAAGTAATTTGAGGTACCTGGTGTTCTCAGGC-3'
Primer for amplifying P4503A4 0.9Kb fragment
1A1
5'-CCTCTAGAAATGCTTTTCCCAATCTCCATG-3'
5'-CCAATCACTGTGTCGAGCTCCTCTTGGATC-3'
Primer for amplifying P4501A1 1.0Kb fragment
5'-GATCCAAGAGGAGCTCGACACAGTGATTGG-3'
5'-GGGCTCTCAAGCACCTAAGAGCGCAGCTGC-3'
Primer for amplifying P4501A1 0.5Kb fragment
2A6
5'-GCTTCTAGAATGCTGGCCTCAGGGATGCTTC-3'
5'-CGTGGAGGTTGACGTGAACTGGAAGATTC-3'
Primer for amplifying P4502A6 0.6Kb fragment
5'-GAATCTTCCAGTTCACGTCAACCTCCACG-3'
5'-AGACCTGGTACCGCACAGCCCTCGCTCAG-3'
Primer for amplifying P4502A6 0.9Kb fragment

Fig. 2

Primer for amplifying P4502B6 1.5Kb fragment

2B6 5'-CCTCTAGAAAATGGAACTCAGCGTCCTCCT-3'
5'-GGGGATCCTGAATGACCCTGGAATCCTTTG-3'

Primer for amplifying P4502C8 1.5Kb fragment

2C8 5'-GAAGAGAAGTCTAGAATGGAACCTTTGTGGTCC-3'
5'-ATAGCAGATCGGCAGCCAGATGGGCTAGCATTC-3'

Primer for amplifying P4502C18 0.9Kb fragment

2C18 5'-AGTCTAGAATGGTACCAGCTGTGGCTCTGG-3'
5'-CCCCAACATATCAGTTACAGTGGCTATCAAGC-3'

Primer for amplifying P4502C18 1.4Kb fragment

5'-CCCGATTATTGGAAATATCCTGCAGTTAGATG-3'
5'-ACAGCACAGGAGCAGCCAAACTATCTGCC-3'

Fig. 3

2C19 The sequence shown by 5'- .. -3' is described in SEQ ID Nos: 20 to 40.

2D6 5'-TGTTCAGCCTGCAGCTGGCCTGGAC-3' — Primer for amplifying P4502D6 0.4Kb fragment
5'-AAGCGAGGGTCGTCGTATTCGAAGCG-3'

5'-GCTTCGAATACGACGACCCTCGCTTCCTC-3' — Primer for amplifying P4502D6 0.9Kb fragment
5'-ACTAGGTACCCCATTCTAGCGGGGCACAG-3'

3A4 (An artificial fused enzyme) — Primer for amplifying P4503A4 XbaI-XhoI fragment

5'- AATCTAGAAATGGCTCTCATCCCAG - 3'
5'- AGGACTCGAGCGGCTCCACTTACGGTGCCATCCC - 3'

Fig. 4

EP 0 644 267 A2

(1) Linker for cloning 1A2

```
5'-AGCTTAAAAAAATGGCATTGTCCCAGTCTGTTCCCTTCTCGGCCACAGAGCT-3'
3'-    ATTTTTTTACCGTAACAGGGTCAGACAAGGGAAGAGCCGGTGTC    -5'
```

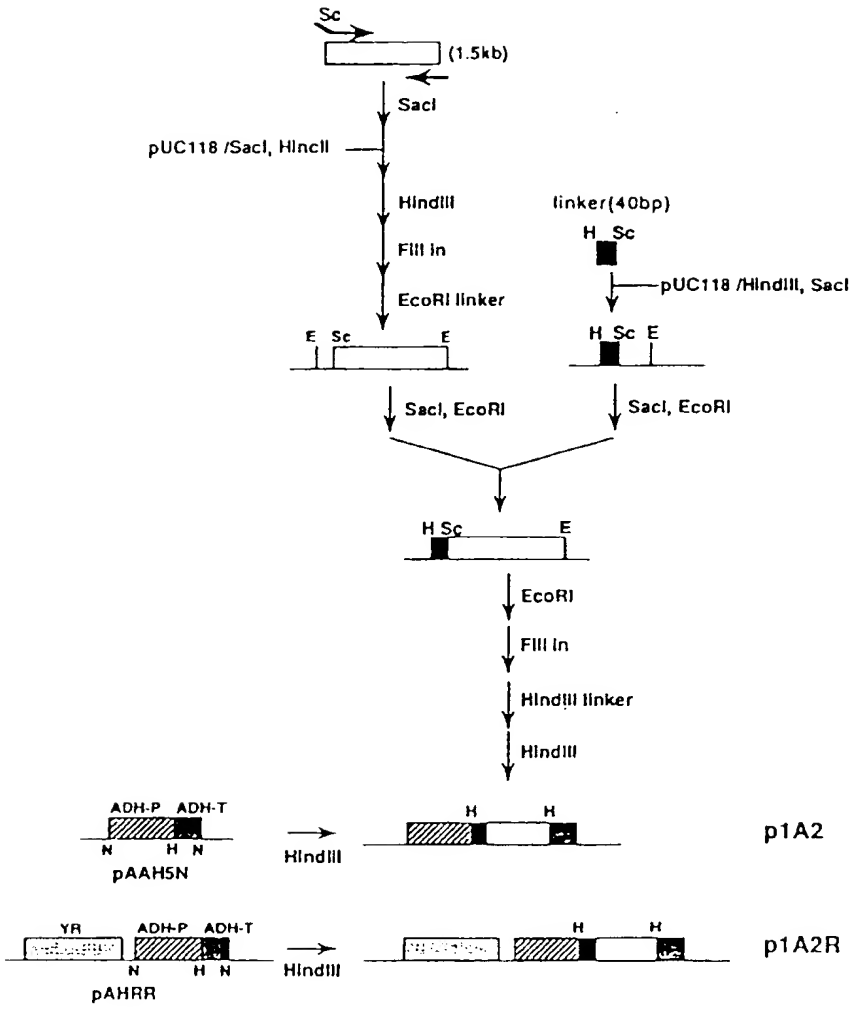
(2) Linker for cloning 2D6

```
5'-CTAGATATGGGGCTAGAAGCACTGGTGCCCCTGGCCGTGATAGTGG-3'
3'-    TATACCCCGATCTTCGTGACCACGGGGACCGGCACTATCACC-5'


5'-CCATCTTCCTGCTCCTGGTGGACCTGATGCACCGGCGCCAACGCTGGGCTGCACGCTACCCACCAGGCCCCCTGCCACTGCCCGGGCTGCA-3'
3'-GGTAGAAGGACGAGGACCACCTGGACTACGTGGCCGCGGTTGCGACCCGACGTGCGATGGGTGGTCCGGGGGACGGTGACGGGCCCG    -5'


5'-GGGCTGGGCAACCTGCTGCATGTGGACTTCCAGAACACACCATACTGCTTCGACCAGTTGCGGCGCCGCTTCGGGGACGTGTTCAGCCTGCA-3'
3'-CCCGACCCGTTGGACGACGTACACCTGAAGGTCTTGTGTGGTATGACGAAGCTGGTCAACGCCGCGGCGAAGCCCCTGCACAAGTCGG    -5'
```

Fig. 5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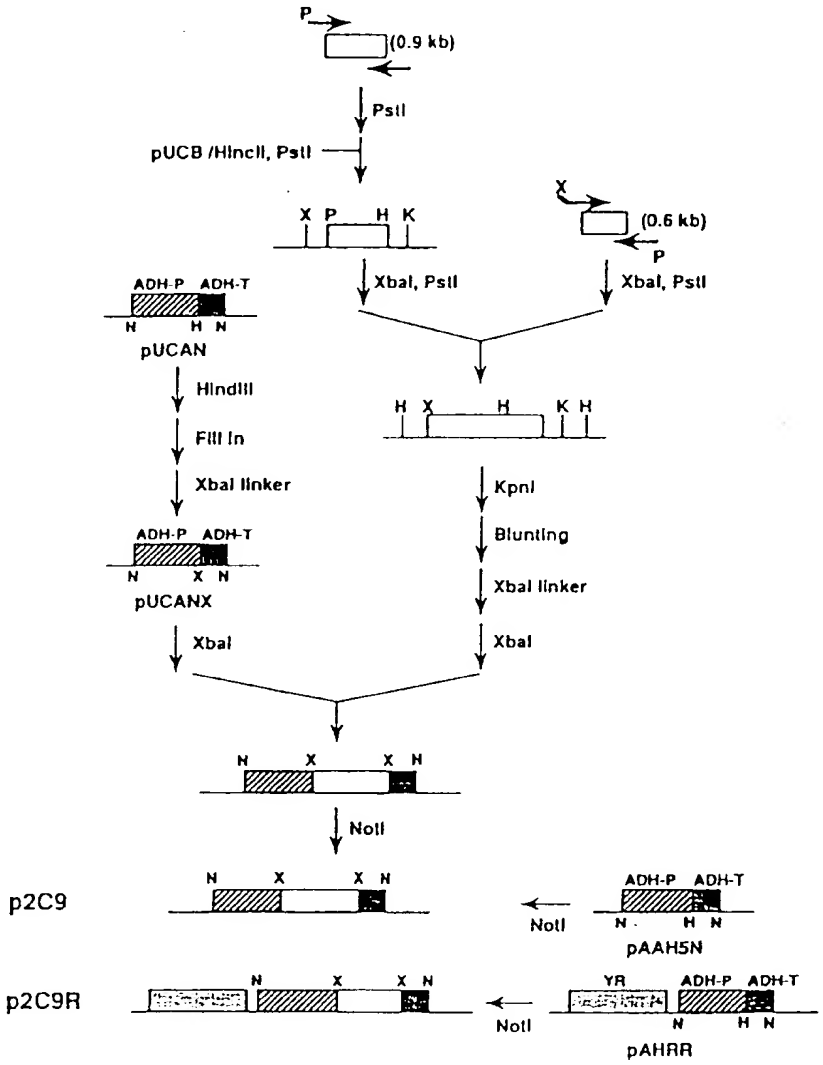
SacI
pUC118 /SacI, HincII
HindIII
Fill in
EcoRI linker
linker(40bp)
H Sc
pUC118 /HindIII, SacI
E Sc E
H Sc E
SacI, EcoRI
SacI, EcoRI
H Sc E
EcoRI
Fill in
HindIII linker
HindIII
ADH-P ADH-T
N H N
pAAH5N
HindIII
H H
p1A2
YR
ADH-P ADH-T
N H N
pAHRR
HindIII
H H
p1A2R

Fig. 6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pUCB /HincII, PstI
X P H K
X
(0.6 kb)
P
ADH-P ADH-T
N H N
pUCAN
XbaI, PstI
XbaI, PstI
HindIII
Fill In
XbaI linker
H X H K H
KpnI
Blunting
XbaI linker
ADH-P ADH-T
N X N
pUCANX
XbaI
XbaI
N X X N
NotI
p2C9
N X X N
NotI
ADH-P ADH-T
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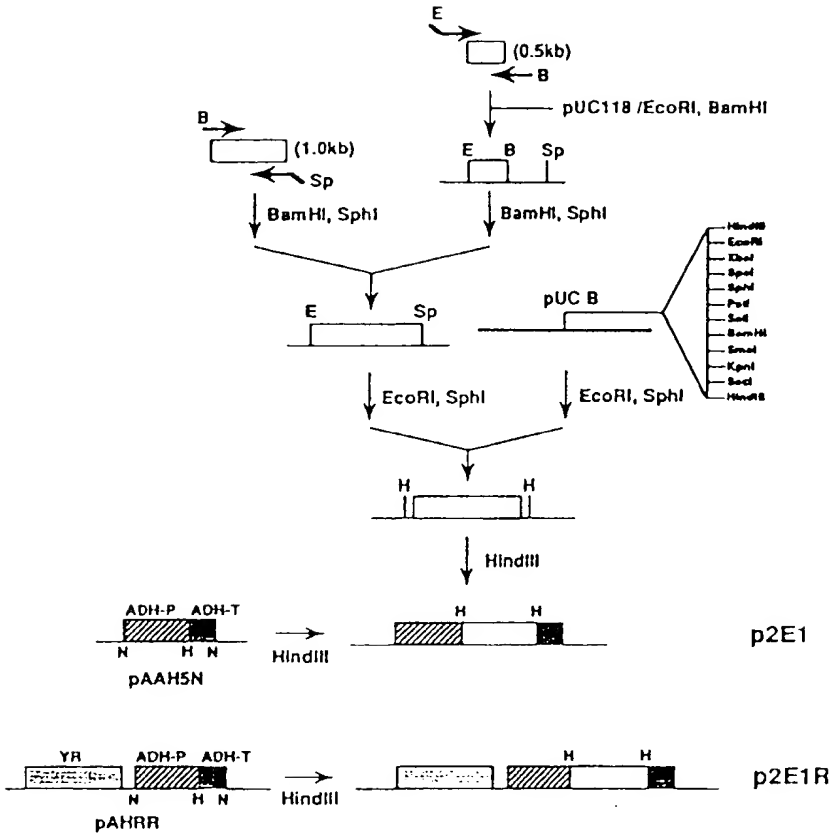
pAAH5N
p2C9R
N X X N
NotI
YR ADH-P ADH-T
N H N
pAHRR

Fig. 7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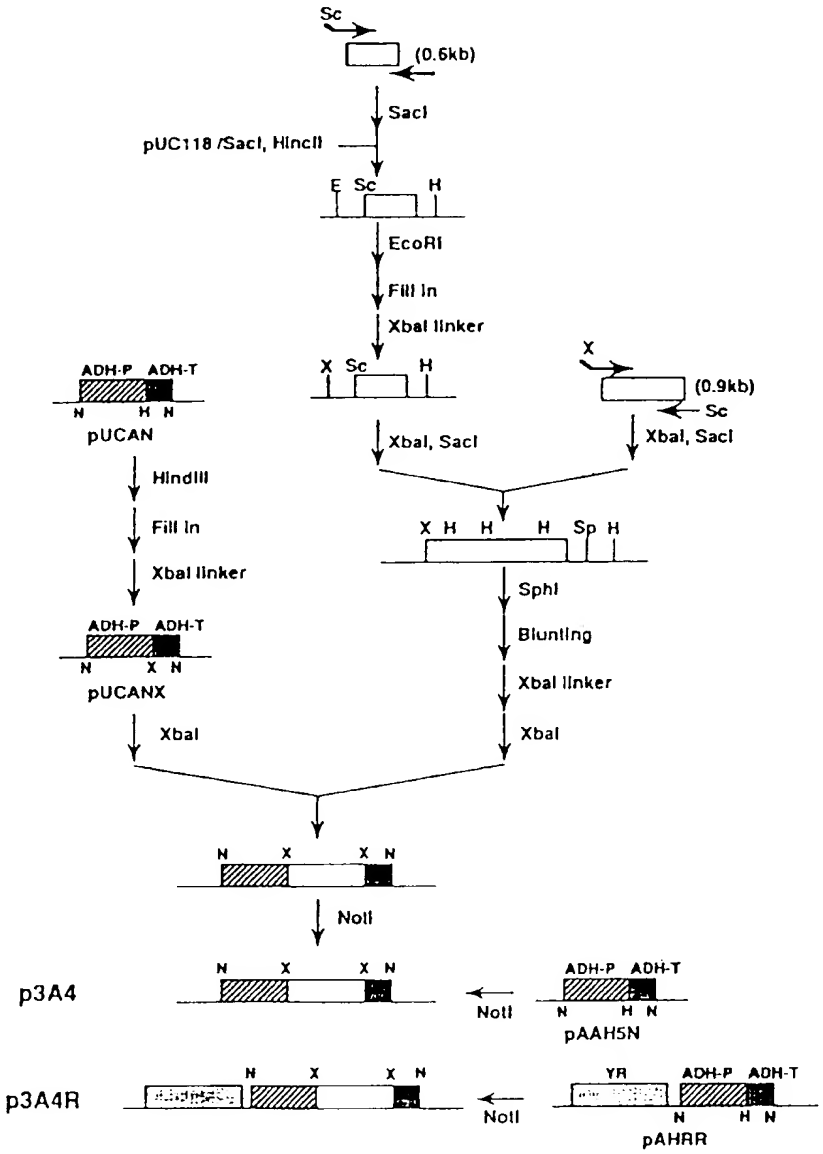
(0.5kb)
B
pUC118 /EcoRI, BamHI
B
(1.0kb)
Sp
E B Sp
BamHI, SphI
BamHI, SphI
E Sp
pUC B
EcoRI, SphI
EcoRI, SphI
H H
HindIII
ADH-P ADH-T
N H N
pAAH5N
HindIII
H H
p2E1
YR
ADH-P ADH-T
N H N
pAHRR
HindIII
H H
p2E1R

Fig. 8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SacI
pUC118 /SacI, HincII
E Sc H
EcoRI
Fill in
XbaI linker
X Sc H
X
(0.9kb)
Sc
ADH-P ADH-T
N H N
pUCAN
XbaI, SacI
XbaI, SacI
HindIII
Fill in
XbaI linker
X H H H Sp H
SphI
Blunting
XbaI linker
ADH-P ADH-T
N X N
pUCANX
XbaI
XbaI
N X X N
NotI
p3A4
N X X N
NotI
ADH-P ADH-T
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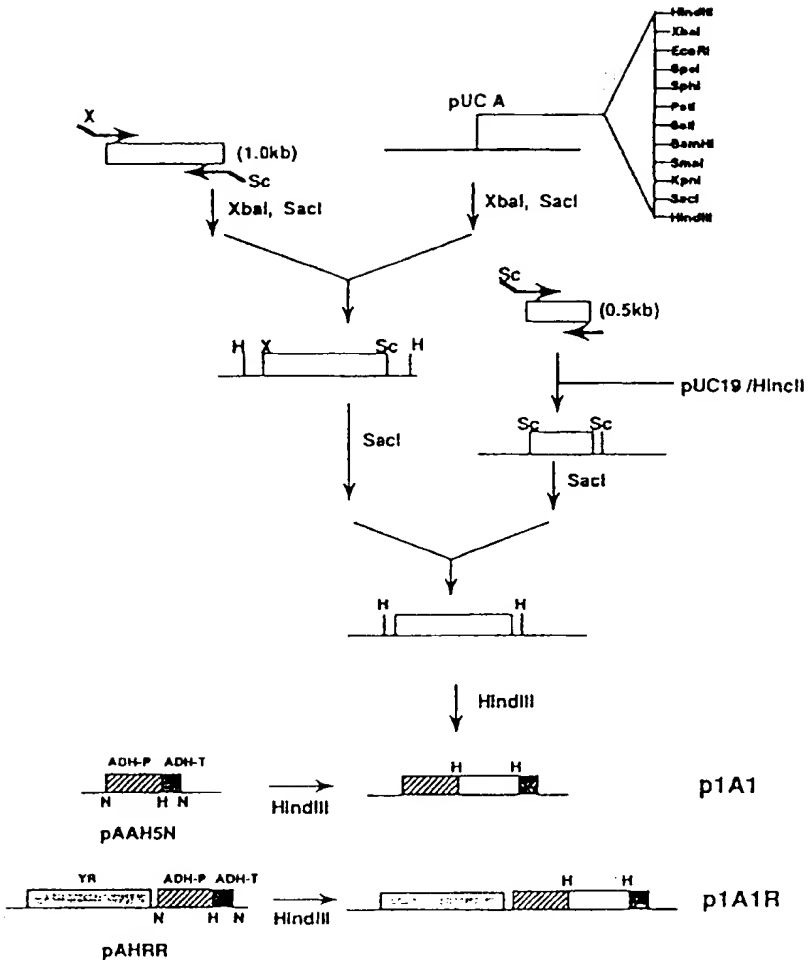
p3A4R
N X X N
NotI
YR ADH-P ADH-T
N H N
pAHRR

Fig. 9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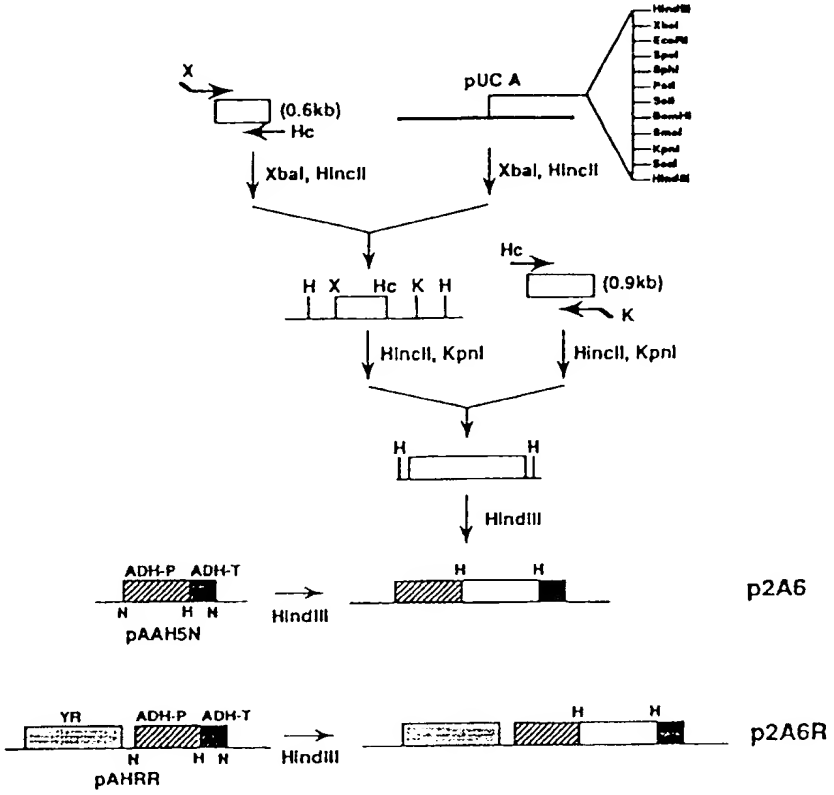
(1.0kb)
Sc
XbaI, SacI
pUC A
XbaI, SacI
Sc
(0.5kb)
H X Sc H
pUC19 /HincII
SacI
Sc Sc
SacI
H H
HindIII
ADH-P ADH-T
N H N
HindIII
H H
p1A1
pAAH5N
YR
ADH-P ADH-T
N H N
HindIII
H H
p1A1R
pAHRR

Fig. 10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(0.6kb)
Hc
pUC A
XbaI, HincII
XbaI, HincII
H X Hc K H
Hc
(0.9kb)
K
HincII, KpnI
HincII, KpnI
H H
HindIII
ADH-P ADH-T
N H N
pAAH5N
HindIII
H H
p2A6
YR
ADH-P ADH-T
N H N
pAHRR
HindIII
H H
p2A6R

Fig. 11

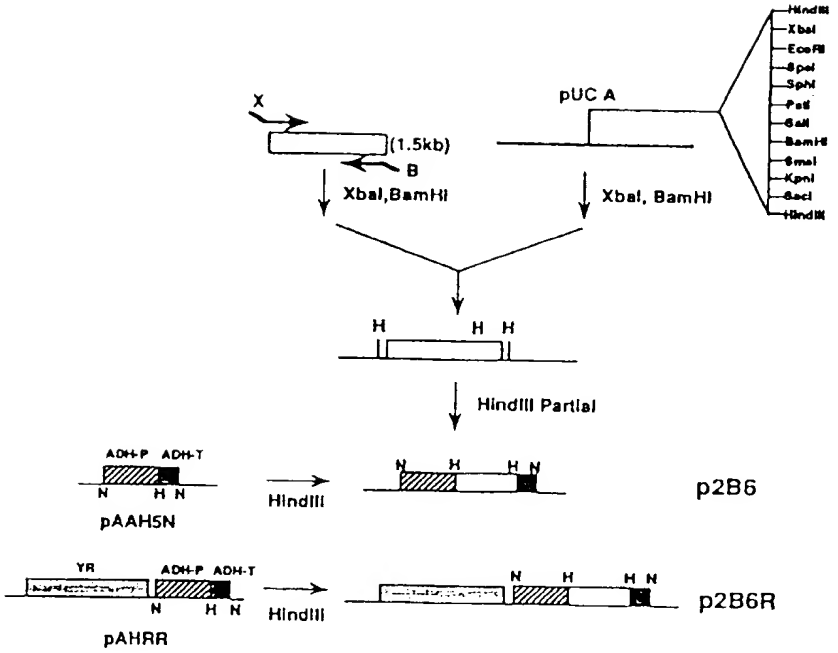

X
(1.5kb)
B
XbaI,BamHI
pUC A
XbaI, BamHI
HindIII
XbaI
EcoRI
SpeI
SphI
PstI
SalI
BamHI
SmaI
KpnI
SacI
HindIII
H
H H
HindIII Partial
ADH-P ADH-T
N
H N
pAAH5N
HindIII
N H H N
p2B6
YR
ADH-P ADH-T
N
H N
pAHRR
HindIII
N H H N
p2B6R

Fig. 12

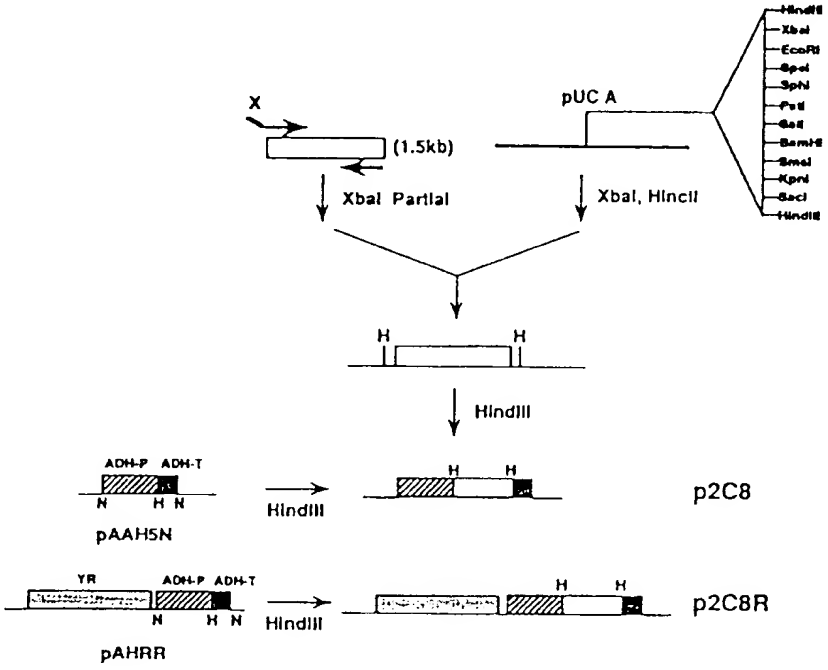
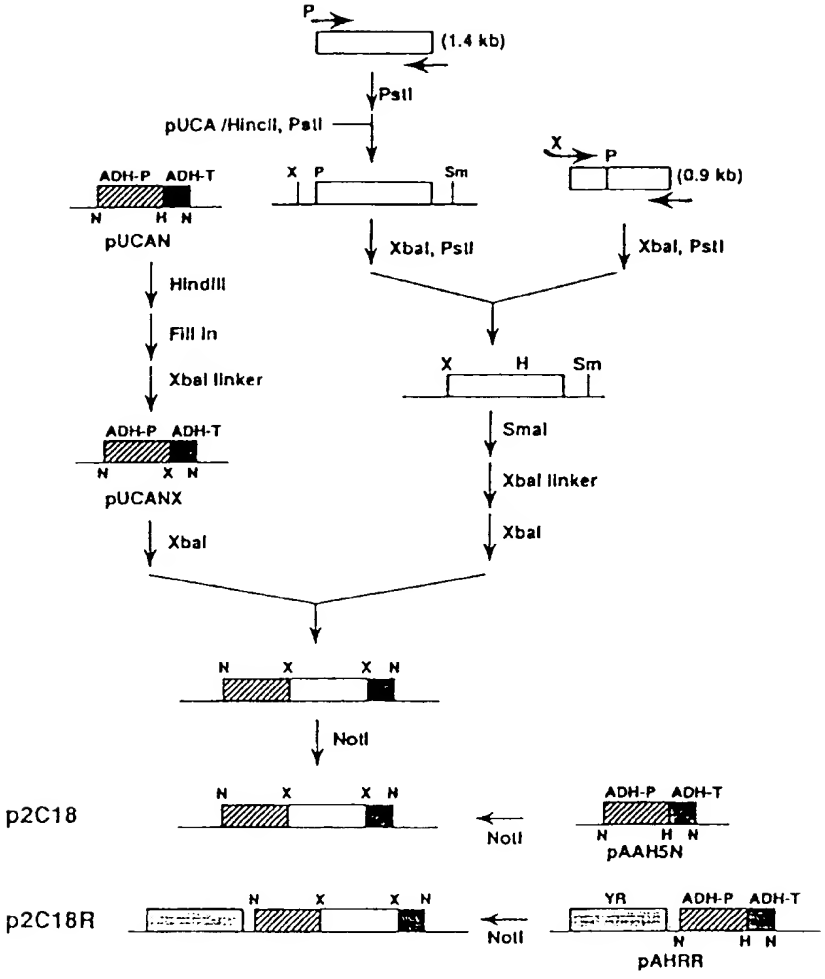

X
(1.5kb)
pUC A
XbaI Partial
XbaI, HincII
HindIII
ADH-P ADH-T
HindIII
p2C8
pAAH5N
YR
ADH-P ADH-T
HindIII
p2C8R
pAHRR

Fig. 13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pUCA /HincII, PstI
X
P
(0.9 kb)
ADH-P ADH-T
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pUCAN
X P Sm
XbaI, PstI
XbaI, PstI
HindIII
Fill In
XbaI linker
X H Sm
SmaI
ADH-P ADH-T
N X N
pUCANX
XbaI linker
XbaI
XbaI
N X X N
NotI
p2C18
N X X N
NotI
ADH-P ADH-T
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N X X N
NotI
YR
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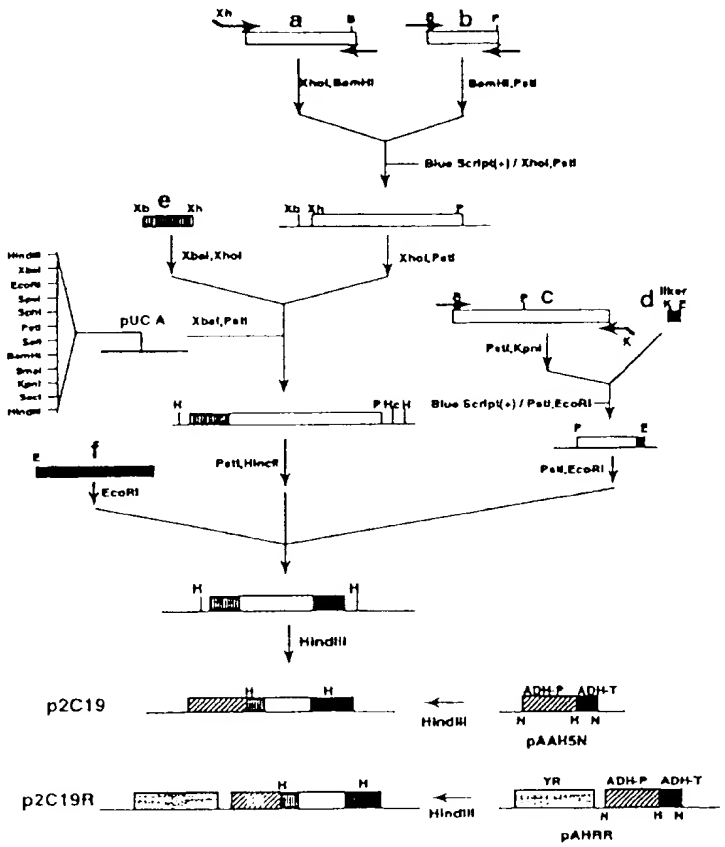
N H N
pAHRR

Fig. 14


a
b
c
d
e
f
XhoI,BamHI
BamHI,PstI
Blue Script(+) / XhoI,PstI
XbaI,XhoI
XhoI,PstI
pUC A
XbaI,PstI
PstI,KpnI
Blue Script(+) / PstI,EcoRI
PstI,HincII
PstI,EcoRI
EcoRI
HindIII
p2C19
HindIII
ADH-P
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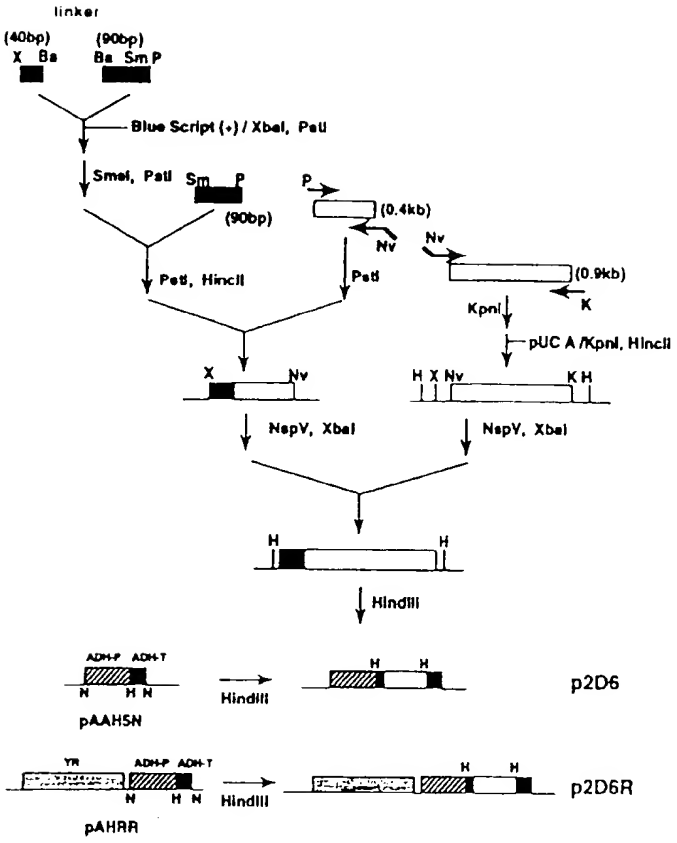
HindIII
YR
ADH-P
ADH-T
pAHRR

Fig. 15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X Ba
(90bp)
Ba Sm P
Blue Script (+) / XbaI, PstI
SmaI, PstI
Sm P
(90bp)
PstI, HincII
P
(0.4kb)
Nv
PstI
Nv
(0.9kb)
K
KpnI
pUC A /KpnI, HincII
X Nv
H X Nv K H
NspV, XbaI
NspV, XbaI
H H
HindIII
ADH-P ADH-T
N H N
pAAH5N
HindIII
H H
p2D6
YR ADH-P ADH-T
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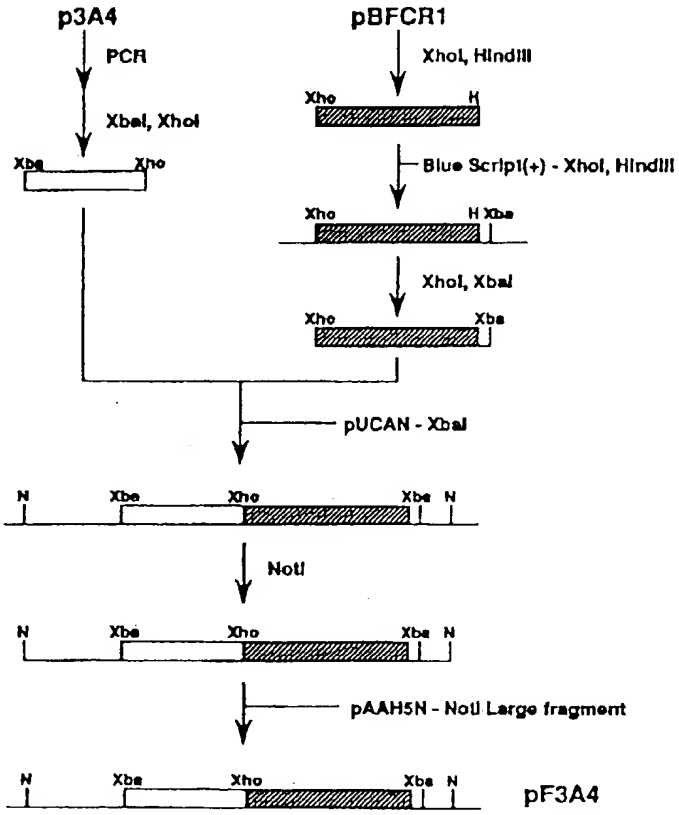
pAHRR
HindIII
H H
p2D6R

Fig. 16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PCR
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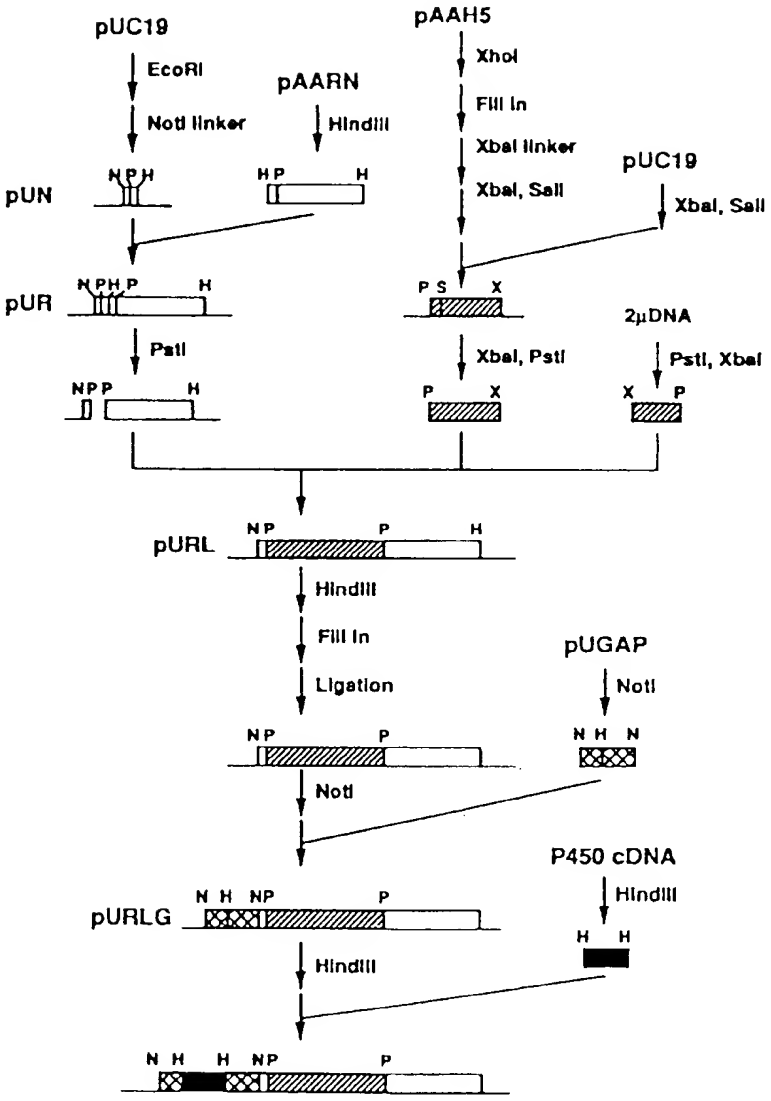
Xba
Xho
pBFCR1
XhoI, HindIII
Xho
H
Blue Script(+) - XhoI, HindIII
Xho
H Xba
XhoI, XbaI
Xho
Xba
pUCAN - XbaI
N
Xba
Xho
Xba
N
NotI
N
Xba
Xho
Xba
N
pAAH5N - NotI Large fragment
N
Xba
Xho
Xba
N
pF3A4

Fig. 17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NotI linker
pAARN
HindIII
pUN
N P H
H P H
pAAH5
XhoI
Fill In
XbaI linker
XbaI, SalI
pUC19
XbaI, SalI
pUR
N P H P H
P S X
2μDNA
PstI
XbaI, PstI
PstI, XbaI
N P P H
P X
X P
pURL
N P P H
HindIII
Fill In
Ligation
pUGAP
NotI
N P P
N H N
NotI
P450 cDNA
HindIII
pURLG
N H NP P
H H
HindIII
N H H NP P

Fig. 18